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I. LISTER AND WIRING THE PATELLA.

THE memory of Lord Lister as the introducer of aseptic surgery is immortal. The memory of Lister as a bold and successful surgeon is already perishing. In 1870 the treatment of transverse fracture of the patella was beginning to attract attention. The older practice was to put the patient to bed, raise the injured leg on an inclined plane to relax the quadriceps muscle, and allow fibrous union to take place—a matter of six to eight weeks. The result was a gap of varying size which tended to increase with use. The leg, however, was useful and the patient was able to follow even so trying an occupation as that of an omnibus conductor at a time when he had to stand for long hours on a 'monkey board' holding on by a strap. More daring surgeons sought to get closer union by means of Malgaigne's hooks—a pair of sharp-pointed double hooks connected by a spring. They were inserted through the skin into the upper and lower fragments. The punctures often suppurated, the joint became involved, and the leg had to be amputated in the lower third of the thigh. A few adventurous surgeons brought the fragments together by a subcutaneous circumferential suture of silver wire.

It was a great experiment, therefore, and worthy, his contemporaries thought, of the utmost reprobation when Lister opened the knee-joint and passed a stout silver wire through the two fragments. He says that he had long been looking for a fractured patella with the intention of wiring it, but had been anticipated by [Sir] Hector Cameron, a former house surgeon and then Surgeon to the Glasgow Infirmary, who performed the operation successfully and without suppuration on March 5, 1877.

"In October of the same year," Lister continues, "a patient with transverse fracture of the patella was admitted under my care in King's College Hospital. He was a man of forty years of age, who, while riding on horseback, had his horse stumble and fall. He was thrown over the horse's head, falling on the right knee. He could not rise and was brought to the hospital. In the first instance, I attempted with this patient to bring the upper fragment down, so that it should be in contact with the lower. For

this purpose I applied an apparatus into the details of which I need not enter further than to say that it was so arranged that the upper fragment by means of weights and pulleys was drawn down. Four days later, however, I found that there was still a quarter of an inch interval between the fragments, and I suggested to the patient the operation of cutting down and applying the wire suture. This, however, he would not then consent to and preferred returning home to be under the care of his ordinary medical attendant. Eight days later—or fourteen days after the accident—he was readmitted, expressing a wish to be operated upon.

"On 26th October I accordingly proceeded to operate, making a vertical incision about two inches in length over the patella exposing the fragments which were then one inch apart. My inability to bring down the upper fragment into contact with the lower became explained when the parts were exposed; for there were found between the fragments extremely firm coagula with fibrous tissue, fascial and periosteal, mingled with them, constituting so firm a mass as to make it quite impossible for the two fragments to be brought into contact. The clots having been completely cleared away from between the fragments and from the interior of the joint, I applied a common bradawl in the middle line of the patella drilling each fragment obliquely so as to bring out the drill upon the broken surface a little distance from the cartilage. Pretty stout silver wire was then passed through the drilled openings and the fragments thus strung upon it were pushed firmly home and so brought accurately into apposition.

"Before they were brought together, however, an arrangement was made for the drainage of the joint. This was done on the same principle in all the cases that I have to record and I may therefore describe the matter once for all. A pair of dressing forceps with blades closed was introduced from the wound made into the anterior part of the joint to the most dependent part of the outer aspect of the articulation. The instrument was then forcibly thrust through the synovial membrane, the fibrous capsule and the fascia until the point of the forceps was felt under the skin. An incision was then made with a knife through the skin upon the end of the dressing forceps, so as to allow it to protrude. The blades of the forceps were then expanded so as to enlarge the opening which they had made in the deeper structures without risk of causing hæmorrhage. The drain was then seized in the forceps that protruded through the wound and drawn into the joint.

"The ends of the wire were now twisted together and the twisted ends brought out at the wound which was closed with sutures and a small drain inserted. I need hardly say that in this case, as in Dr. Cameron's, antiseptic treatment was employed.

"It is unnecessary for me to enter into details as to the progress of this case. We have here the temperature-chart for as long as it was thought worth while to have it recorded, and you will see that it indicates, after a little temporary disturbance immediately after the operation, an entirely afebrile condition. The wounds healed without any suppuration. At the end of eight weeks the wire was removed by an incision through the cicatrix. Eight days later the wound made for the removal of the wire had healed. At the end of ten weeks from the operation the patient was allowed to get

up and, though no passive movement had been employed, he could move the limb freely through an angle of about thirty degrees. Two days later he was discharged and unfortunately nothing has been heard of him since. I saw him once in a cart a few days after he was dismissed but I have not been able to learn any further tidings of him. This, I believe, is the first instance of a recent case of fracture of the patella being treated by wire-suture antiseptically applied. My next case occurred two years later."

[From a clinical lecture delivered at King's College Hospital on Dec. 10, 1877. Reported in the *Lancet*, 1878, i, 5.]

A CONTRIBUTION TO THE STUDY OF PULMONARY LOBECTOMY.*

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The excision of a lobe of the lung of necessity involves the severance of its connections, normal and abnormal, with the walls of the cavity in which it is confined; and present-day methods of pulmonary lobectomy—the Brunn-Shenstone[1, 2] and Alexander operations may be taken as types—are dependent, amongst other things, on the feasibility of dividing pleural adhesions when these exist. As a rule, the division is easily effected by dissection with scissors or gauze.†

Not very uncommonly, however, the adhesive pleurisy will be found to have progressed so far that, over a more or less extensive area, the lung and chest wall have become integral with one another, so that no method of separation, other than frank section with a knife, is adequate to effect their division. In these circumstances the freeing of the lung may prove a severe task for the surgeon; it certainly adds considerably to the length of the operation and the burden of the patient, and it entails the risk of wounding the lung and so allowing the escape of highly infective material.

It is suggested that these technically more formidable cases might be dealt with by ligature of the pedicle of the lobe, the gangrenous lung being left *in situ* until it had begun to separate by a line of demarcation between the living and the dead tissues. Before this method can be applied to human surgery it is necessary to estimate the ability of the animal organism to tolerate the presence in the chest cavity of a mass of dead lung.

It was primarily with this object in view that the present investigation was undertaken. The research was carried out in cats and involved three operative stages: (1) To attempt to cause dense pleural adhesions, so that the conditions met with in practice might be imitated; (2) To bring about gangrene of a lobe by ligation of its pedicle; (3) After intervals varying in different animals, to attempt the removal of the dead tissue from within its living surroundings.

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* From the Department of Surgery, University of Manchester.

† Alexander's[3] technique, which has a bearing on what follows, calls for a short description. At the first stage pleural adhesions are broken down by the finger or divided with scissors. The whole lung and the parietal pleura are then gently rubbed over with gauze. At the second stage the newly-formed adhesions of the diseased lobe are broken down by the finger, the pedicle is doubly ligatured, and, after provision has been made for irrigation and drainage, the lobe is brought out of the wound, which is sutured round the projecting lung. Four days later the wound is opened up completely, and, in due course, the protruding lobe separates, leaving a bronchial fistula.

GENERAL DESCRIPTION OF EXPERIMENTAL METHOD.

The anæsthetic used throughout was ether, with or without ¼ mgrm. of atropine. After induction of surgical anæsthesia, a No. 8 English, gum-elastic catheter was introduced into the trachea with the aid of a simple laryngeal spatula and a headlight. Strong traction on the tongue renders exposure of the larynx easy in the cat. The administration of ether was continued by positive ventilation, and the chest was opened through an intercostal incision, the ribs being spread by means of a mastoid retractor.

At the first stage various means of bringing about the desired adhesions were applied, and the opportunity was taken to place a double ligature of ordinary sewing cotton loosely in position round the pedicle of the selected lobe, the ends of the ligature being left under the skin in order to facilitate subsequent identification. At the second stage the ligature was traced to the hilum and there tightly tied so as to deprive the lobe entirely of its blood-supply. Care was taken to reduce the separation of adhesions to the minimum compatible with accessibility of the pedicle. The lobe was left undisturbed and the chest was closed with or without drainage. Reference will be made later to the question of drainage, but it may be said here that, as the experiments went on, the necessity for drainage at any stage appeared less and less. Two animals, Nos. 6 and 7, passed through all three stages without having the chest drained at any of them. In one, No. 5, though it was perfectly well, a considerable serous effusion between the diaphragm and the lower lobe was discovered at the third-stage operation, and in another, No. 6, the meshes of the gauze in which the lobe had been wrapped were soaked in serum. Apart from these and the two fatal empyemata, no effusion was discovered in any animal throughout the course of the experiments.

The Experimental Production of Pleural Adhesions.—In the first two animals friction applied to both layers of the pleura by dry gauze and gauze soaked in rectified spirit failed to engender any but negligible adhesions. In the third and fourth cats an attempt to cause obliteration of the pleural cavity by the instillation of Dakin's solution, which Beck[4] has used in dogs to produce adhesive pericarditis, resulted in the death of the animals from sero-fibrinous pleurisy and bilateral empyema respectively. Chlorinated solutions were therefore discarded in the subsequent experiments. Finally recourse was had to a method described by Nissen.[5] He enclosed the lobe in a large-meshed string bag, the neck of which was tied loosely round the pedicle by means of a running noose. In the experiments with which this paper is concerned, Nissen's string bag was at first replaced by a single layer of gauze. This proved bulky and clumsy, and in Cats 7, 8, and 9 the lobe in question was enclosed in a bag of cotton net, made roughly to shape and having a noose to surround the pedicle without compressing it. On the whole, this was a satisfactory method, but the interposition of the gauze or net between the two layers of pleura made the line of demarcation of the living and dead tissues rather different in character from what it would be in human

TABLE SHOWING RESULTS OF EXPERIMENTS.

Cat No.	1st Stage	Result	Interval	2nd Stage	Result	Interval	3rd Stage	Result	Remarks
1	Left upper lobe. Ligature placed in position round pedicle. Whole of both layers of pleura rubbed over with gauze. No drain	Off food for three days. Wound healed by first intention	Days 31	Ligature tightly tied. 3-day tube drain	Very fit next day. Wound healed by first intention	Days 14	Some adhesions, but much open pleural space. Lobe excised. Tube drain	Very fit next day—walking. The wound healed in 8 days	Developed a 'cold' after complete recovery. Well for over 4 months, then died for no apparent reason. P.M.—Shifting of mediastinum to left. No cause for death found
2	Ligature left loose round left upper lobe pedicle. Whole pleura rubbed over with gauze soaked in spirit. No drain	Wound healed by first intention	15	Ligature tightly tied. Further ligature applied and pedicle cut between them. Practically no adhesions, so that lobe remained freely mobile in pleural cavity	Good recovery for first week, then developed 'pneumonia'. Steady improvement after 14th day. Little pus from wound but quite healed by end of two weeks	35	Grey sloughed lobe firmly adherent to mediastinum and pericardium. Some force necessary to bring about its separation.	Died a few hours after operation	P.M. — Right heart dilated. Little blood in both pleural cavities, though left pleura intact. Right lower lobe collapsed. It and left lung showed considerable areas of deep congestion
3	Ligature left loose round left upper lobe pedicle. Dakin's solution rubbed over whole pleural cavity. Drain, temporarily closed to prevent pneumothorax	Recovered from operation, but the animal soon lost ground. Free discharge from wound. Died 10 days after operation							P.M.—Sero-fibrinous pleurisy throughout left chest
4	Pulmonary ligament cut and ligature loosely placed round pedicle of left lower lobe. Diaphragm accidentally injured and sutured. Tube drain temporarily tied at free end. Pleural cavity swabbed with eusol	Recovered well for 9 days. About 10th day milky discharge from tube. Condition began to deteriorate on 18th day and animal was destroyed on 22nd day							P.M. — Bilateral empyema. Left lung entirely collapsed
5	Pedicle of left	Uninterrupted	21	Satisfactory ad-	Uncomplicated	9	Collection of fluid	Uninter-	Destroyed 18

bed with eusol									
5	Pedicle of left lower lobe loosely encircled by ligature. Lobe enclosed in single layer of gauze. Tube drain temporarily tied at free end	Uninterrupted recovery. No discharge from tube, which was removed on 9th day	21	Satisfactory adhesions of whole lower lobe. Ligature tightly tied. 4-day drain	Uncomplicated recovery. Wound healed in 8 days	9	Collection of fluid between lung and diaphragm. Lobe did not separate easily. Pedicle divided and lobe removed. Tube drain temporarily closed	Uninterrupted recovery. Tube out on 12th day	Destroyed 18 weeks after 3rd stage. Mediastinum and right lung had shifted over to left. Upper lobe occupied centre of left pleural cavity. Some of space occupied by deposition of fat
6	Pedicle of left lower lobe loosely encircled by ligature. Lobe wrapped in gauze. No drain	Recovered well	14	Extensive adhesions. Ligature tightly tied. No drain	Good recovery. (*Fig.* 375)	14	Separation of lobe with difficulty. Pedicle cut and gangrenous lobe removed. Extensive wound of right pleura. Air-tight closure	Uninterrupted recovery	Animal destroyed 7½ weeks after 3rd stage. Shifting of mediastinum and right lung as in Cat 5 (*see Figs.* 376, 377)
7	Pedicle of right lower lobe loosely encircled by ligature. Lobe wrapped in net bag, neck being loosely tied round hilum. Bag too small for lobe. No drain	Recovered well	28	Good adhesions, but lobe not everywhere in contact with chest wall. Ligature tightly tied. Healthy lobe injured, but small breach ligatured. No drain	Uninterrupted recovery	7	Adhesions separrated fairly easily, but small hole torn in left pleura. Pedicle divided & gangrenous lobe removed No drain	Uninterrupted recovery	Animal alive and well at time of writing, 17 weeks after 3rd stage
8	Pedicle of left lower lobe loosely encircled by ligature. Lobe wrapped in net bag of ample size. No drain	Good operative recovery, but did not eat well and lost some weight	14	Lobe completely expanded and everywhere adherent. Ligature tightly tied. No drain	Good operative recovery, but animal refused food. Artificial feeding tried, but died on 4th day after 2nd stage				Lower lobe gangrenous & everywhere adherent to upper lobe and chest wall. Specimen shown in *Fig.* 374
9	Pedicle of right lower lobe loosely encircled by ligature. Lobe wrapped in net bag of ample size. No drain	Uninterrupted recovery	14	Lobe rather collapsed. Adhesions of lower to other lobes, but not to chest wall. Ligature tightly tied. No drain	Good recovery	9	Laceration of healthy lobes during separation and removal of gangrenous lower lobe after division of pedicle. Open drain to prevent tense pneumothorax	Died a few hours after operation	P.M.—Little blood in both pleural cavities. Right heart dilated. Both lungs congested

surgery, and this factor, together with the extreme delicacy of the tissues of the cat, made it impossible to bring about conditions comparable to those with which the practising surgeon would be faced.

Effects of the Presence of a Necrotic Lobe inside the Thorax.—Of the seven animals in which a lobe was devascularized, six recovered. In the fatal case, Cat 8, there had been some loss of appetite after the first stage, and after the second, though it made a good operative recovery, the animal refused all nourishment. In spite of attempts to feed it by means of a pipette, it died on the fourth day. *Figs.* **373**, **374** show a drawing of the specimen, which had been preserved in Kaiserling solution. Three of the other six cats were so little inconvenienced by the second-stage operation that, on the following day, it was impossible to tell from their general appearance that they had undergone an operation at all. Two of the others lay quietly in their cages for a day or two, but took their food well and made uncomplicated recoveries. In the remaining case, Cat 2 (in which no adhesions had formed as a result of the first stage operation), the pedicle was completely divided at the second stage, so that the separated (upper) lobe remained as a free slough in the chest cavity. A tube drain was removed on the fourth day and, though there was a slight discharge of pus from it, the wound had completely healed in a fortnight. For the first week the animal progressed well, but in the second its condition deteriorated, probably as the result of a pneumonia. After the fourteenth day progress was rapid and the animal thrived, the dead lung being allowed to remain for thirty-five days before the third stage was undertaken.

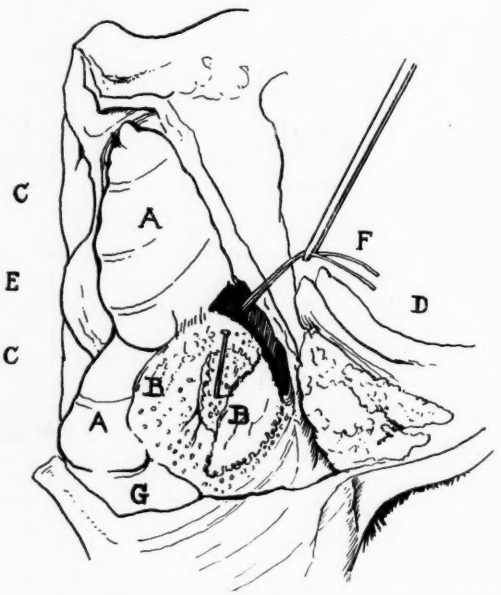

FIG. 373.—Cat 8. Gangrenous left lower lobe. Key to coloured illustration on p. 565. A, Left upper lobe; B, Left lower lobe—a portion of the net bag covering has been turned aside to expose the gangrenous lung tissue; C, Right lung; D, Portion of adherent thoracic wall turned aside; E, Pericardium; F, Ligature round pedicle of left lower lobe; G, Diaphragm.

Third-stage Operation—Removal of the Necrotic Lobe.—Six cats, Nos. 1, 2, 5, 6, 7, and 9, were submitted to the third-stage operation. Two, Nos. 2 and 9, died as the result of it. It was hoped that information gained from this part of the work would indicate the most favourable time after the second stage at which to remove the affected lobe. In order to obtain this knowledge, however, it would be necessary to use other methods of producing adhesions, and animals the consistence of whose tissues approximates more nearly than it does in cats to that of human tissues.

Reference to the table shows that in Cats 5, 6, 7, and 9, intervals of 9, 14, 7, and 9 days respectively were allowed to elapse between the performance

of the second and third stages. No noteworthy difference in the ease of pneumolysis was observed to result from varying the interval. Separation was difficult in all the animals, the gauze or net covering having brought about firm adhesions, so that injury to the delicate lung or the filmy pleura was almost inevitable. In Cats 6 and 7, though every care was exercised, a hole was torn in the opposite pleura, but, in spite of the double pneumothorax, air-tight closure of the chest enabled the animal to breathe without

FIG. 374.—Cat 8. Gangrenous left lower lobe. Drawing made from the animal, which died four days after the second-stage operation. The figure shows the condition which in six other animals was compatible with recovery.

embarrassment, and the post-operative course caused no anxiety. The line of cleavage was always made between the gauze covering of the dead lobe and the neighbouring healthy tissues. Nissen found separation to be easy, but he first made an opening into the net bag and extracted out of it the lobe which it enclosed.

Of the fatal cases, in Cat 2, to which reference has been made above, what had been a free slough was found, after five weeks' sojourn in the pleural

cavity, to have become firmly adherent to the mediastinum and pericardium, so that it could only be separated with great difficulty. In spite of its tough consistence, it tore in two pieces during the process of extraction. The animal died a few hours after the operation. In Cat 9, in which the right lower lobe had been enclosed in a net bag, adhesions had formed only between the devascularized and the neighbouring healthy middle and the upper lobes, and not to the chest wall. In the separation of these adhesions, nine days after the second stage, considerable laceration was caused to the healthy

FIG 375.—Cat 6. Eleven days after second-stage operation. The figure shows the consolidated (gangrenous) left lower lobe, with a small effusion.

lobes. An open tube drain was left in the chest, to prevent any danger of tense pneumothorax. Death took place shortly after the operation. The post-mortem appearances were the same in both animals. Dilatation of the right heart and congestion of both lungs pointed to respiratory failure as the cause of death, though the mechanism of its production was not clear.

The late changes in position of the thoracic contents which occur as the result of lobectomy were seen after death in Cats 1, 5, and 6, and are pictured in the living animal in *Figs.* **376, 377.** These changes have been studied by Morrison[6] and do not call for a detailed description here.

DISCUSSION.

The investigations which form the subject of this paper leave no doubt concerning the possibility of survival of an animal in whose closed pleural cavity there is a necrotic pulmonary lobe. They lend support to the proposal to practise a two-stage lobectomy in man, by depriving the lobe of its blood-supply and later shelling out the gangrenous lobe. It must be borne in mind that the animals used and their lungs had previously been healthy and that

FIG. 376.—Normal cat—for comparison with *Fig.* 377.

a like success might not attend the unthinking application of the same methods to the abscess-riddled lungs of broken-down human patients.

Recent technical developments in pulmonary lobectomy in man have an important bearing on this question. It is long since Sauerbruch ligatured the main branch of the pulmonary artery to the diseased lobe, but during the past two years there have been published accounts of operations in which the whole pedicle has been constricted, the pulmonary tissue being left to slough inside the chest. Thus Nissen,[7] after an extensive pneumolysis, removed a whole lung by this method, and he is quoted by Lagos[8] as using

elastic compression as near the pedicle as possible in those cases in which isolation of the hilum is impracticable. John Alexander,[9] at the second stage of his routine lobectomy, now ligatures the pedicle and closes the chest tightly round a drainage-tube, re-opening the wound and, in certain cases, cutting away the gangrenous lobe on the fourth or fifth day. In that adhesiolysis is in them an essential preliminary, these operations differ from the one which is here suggested, but the feasibility of the latter in man seems assured by the successes which Alexander and Nissen have reported. Such

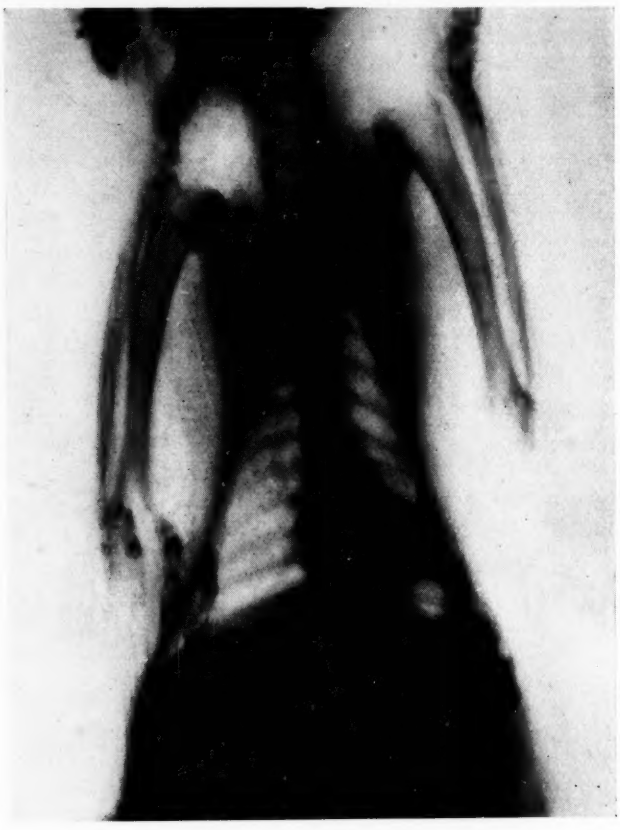

FIG. 377.—Cat. 6. Nine weeks after third-stage operation (removal of left lower lobe). The figure shows falling in of left thorax and mediastinal shift to the left.

an operation would not generally replace more orthodox methods of lobectomy, but would find its special indication in cases which may be grouped as: (1) Those in which the firmness of adhesions between the visceral and parietal pleura renders their separation dangerous or impossible; and (2) Those in which previous drainage to the exterior of abscess or bronchiectatic cavities has fused the lung to the chest wall. The projected operation has the advantage of divisibility into multiple stages and is applicable to those cases in which the surgeon considers it desirable to obliterate the pleural

cavity before excising the lobe; but it would only be practicable where existing accessibility of the hilum or its exposure by dissection permitted isolation and ligature of the pedicle.

SUMMARY.

1. An account is given of experimental work which shows that animals can survive although there is a mass of dead lung in the pleural cavity.

2. The findings support the proposal that it would be possible to remove densely adherent lung by cutting off its blood-supply and allowing it to slough, the extraction of the dead lung being deferred till it had separated by the formation of a line of demarcation between it and its surroundings.

The expenses of this investigation have been met by a grant from the University of Manchester. I desire to express my thanks to Dr. A. D. Macdonald, Reader in Pharmacology in the University, for placing at my disposal the resources of his laboratory, for his continued interest and much personal help; and to Dr. R. S. Paterson, who has taken the X-ray photographs and interpreted them for me.

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MULTIPLE CARCINOMA OF THE COLON: WITH FOUR ORIGINAL CASES.

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MULTIPLE PRIMARY MALIGNANCY: ITS FREQUENCY AND CAUSATION.

Since Billroth published the first authentic cases of multiple primary cancer in 1869 hundreds of contributions have been made to the literature and several large series of cases have been collected. The subject is of sufficient interest in itself, the occurrence of more than one primary malignant growth in the same patient being always something of a phenomenon. Of greater significance is the possibility that these multiple growths may shed light on some of the unsolved problems of cancer pathology.

Incidence of Multiple Cancer.—The literature reveals a striking lack of agreement on the frequency of this condition. Some writers claim that it is rare and that its occurrence is within the limits of coincidence; others maintain that it is common and that factors other than coincidence are concerned in its etiology. This difference is amply illustrated by *Tables I* and *II*, which summarize the incidence of multiple primary growths in some of the larger published lists of cancer autopsies. They show a discrepancy too great to be accidental, and accountable for only by variation of the criteria of multiple malignancy employed by the writers.

The fundamental problem confronting every worker in this field is: What exactly constitutes multiple primary malignancy? Should the growths be histologically distinct and heterogeneous? Must they occur in different organs, systems, or tissues? Should only synchronous growths be included, and should a prolonged interval between metachronous growths disqualify them? Must each tumour be associated with distinct and dissociable metastases?

Criteria based on affirmative replies to these questions are necessarily so severe that only a small proportion of possible cases of multiple primary cancer, whether published or unpublished, could survive them. And it is on such or similar criteria that the 'low-incidence' school, following the example set by Billroth, base their statistics. Thus, Orr[4] agrees with Ewing[10] that there is no etiological relation between multiple malignant tumours, and that their occurrence can be explained by coincidence, while Murray[11] goes so far as to state that one malignant growth actually inhibits the development of a second.

A moment's consideration, however, must show that these criteria are too strict, and that observations based on them are unconvincing. Surely, if two malignant tumours coexist, or follow each other, and it can be definitely

established that one is not a metastasis of the other, they must both be regarded as primary growths. And if, on such basis, multiple primary malignancy proves more common than can be accounted for by chance, then the etiological significance of this phenomenon is worthy of investigation.

Table I.—Statistics of 'Low Incidence' of Multiple Malignancy in Cancer Autopsies.

Author	Total Cancer Autopsies	Cases of Multiple Malignancy	Percentage
Junghanns[1] (1919)	4219	19	0·5
Brandt and Jekabson[2] (1930) ..	2083	11	0·5
Bilello and Montanini[3] (1931) ..	1154	7	0·6
Orr[4] (St. Mary's Hospital) (1930)	1048	8	0·8
Totals ..	8502	45	0·53

Table II.—Statistics of 'High Incidence' of Multiple Malignancy in Cancer Autopsies.

Author	Total Cancer Autopsies	Cases of Multiple Malignancy	Percentage
Hanlon[5] (1931)	950	18	1·9
Egli[6] (1914)	631	16	2·2
Warren and Gates[7] (1932) ..	1078	40	3·7
Medwedjew[8] (1924)	470	20	4·3
Owen[9] (1921)*	3000	143	4·8
Totals ..	6129	237	3·9

* Not strictly an autopsy list.

In this matter I find myself in entire agreement with Warren and Gates,[7] who include under the term 'multiple primary malignancy' all multiple growths except those with a possible metastatic origin, and those which are commonly pluricentric (e.g., multiple skin cancers, bilateral ovarian tumours, multiple myelomatosis, etc.). On this basis they collected 1259 cases of proved multiple primary malignancy from the literature and from their own records. Their rejection of no fewer than 439 of the 628 cases analysed by Major[12] in 1918 is evidence of the strictness of their criteria. The figures quoted by Warren and Gates show, with some certainty, that the incidence of multiple primary malignancy is many times greater than the calculated incidence based on chance. One may add that probably more cases are missed than incorrectly diagnosed. These considerations lead to the conclusion that multiple malignant growths occur much more frequently than can be accounted for by coincidence.

Etiology of Multiple Cancer.—A study of published cases reveals, as one would expect, that the great bulk are multiple carcinomata, showing all

gradations between exactly similar and totally dissimilar growths; a few are carcinoma and sarcoma in different organs, while the rarest are multiple primary sarcomata. Of peculiar interest are the examples of the carcinoma sarcomatodes of Virchow, in which carcinoma and sarcoma are found in the same organ; Warren and Gates found 71 such cases in the literature. In this connection mention may be made of the experiments of Ehrlich and of Russell (quoted by Norbury[13]), who succeeded in changing typical adenocarcinoma in mice into a mixed tumour, and finally into a pure sarcoma.

Accepting the high incidence of multiple malignancy (probably between 3 and 4 per cent of all cancers), a consideration of its etiology leads us to four possible explanations: (1) Implantation (contact or self-infection); (2) Origin from multiple or diffuse precancerous lesions; (3) Individual susceptibility to malignancy, perhaps inherited or familial; (4) Increased susceptibility (diminished immunity) produced by a previous cancer.

1. *Implantation or contact cancers* are common and well known, but they are not examples of multiple primary malignancy. The possibility of implantation does, however, arise in some not obviously contact cancers, and must be taken into account (*see below*).

2. *Pluricentric origin from precancerous lesions* is undoubtedly responsible for some cases (e.g., malignant polyposis of intestine), but it cannot be sustained as a general explanation. Were this the common etiology, one would expect most multiple growths to attack the same organ or system. Actually, the reverse is the case, multiple cancers being mostly encountered in organs unrelated by any system (Warren and Gates,[7] Norbury,[13] Bargen and Rankin[14]).

3. *Individual susceptibility* (perhaps hereditary or familial) is the only explanation capable of general application. Accepting this susceptibility it is not difficult to understand why more than one growth develops, provided there is more than one locus of irritation. This view is supported by Slye's experiments (quoted by Norbury[13]), who found that mice with a cancerous ancestry develop carcinoma following injury which has no effect on control mice of non-cancerous ancestry.

4. Whether or not one cancer produces *increased susceptibility* to a second we have no means of determining. Cuthbert Dukes,[15] writing in 1930, considers that existing statistics fail to settle the question either way. But more recent publications, especially Warren and Gates' painstaking analysis, appear to establish (one hopes beyond dispute) the cardinal fact that *one primary malignant tumour does not inhibit the development of a second.* In other words, that cancer does not confer immunity.

MULTIPLE CARCINOMA OF THE COLON.

It is somewhat surprising to find that while multiple cancer of the gastro-intestinal tract is far from rare (169 cases were collected by Warren and Gates), apparently only 29 authentic cases are reported of multiple growths limited to the colon. In most of the published cases the rectum, stomach, and small gut, in that order of frequency, share the growths with the colon, or harbour them to its exclusion. The occurrence of 4 cases

of multiple colonic growths, out of a total of 54 cases of cancer of the colon attended in the Surgical Unit of this Hospital in the past ten years, must therefore be a unique experience.

A brief description of the cases (hitherto unpublished) is here given :—

Case 1.—**Carcinoma of descending colon. Carcinoma of pelvic colon.**

Female, aged 66 (1929). Occasional diarrhœa and melæna for three and a half years. Radiograms show stasis in the sigmoid colon. Operation revealed an annular malignant stricture at lower end of pelvic colon, and a second distinct carcinoma of descending colon. Inoperable owing to secondary growths along mesentery. Ovarian cyst also present. Transverse colostomy performed. Patient discharged relieved.

Comment.—The long history, and the presence of peritoneal secondaries, and of an ovarian cyst, are noteworthy. Owing to the absence of any indication of the relative ages of the two growths, the possibility of implantation cannot be excluded.

Case 2.—**Four separate cancers of left colon (*Fig.* 378).**

Male, aged 64 (1922). Pain, constipation, and blood in stools (eleven months). Lump felt along iliac colon and another in rectovesical pouch. Operation revealed

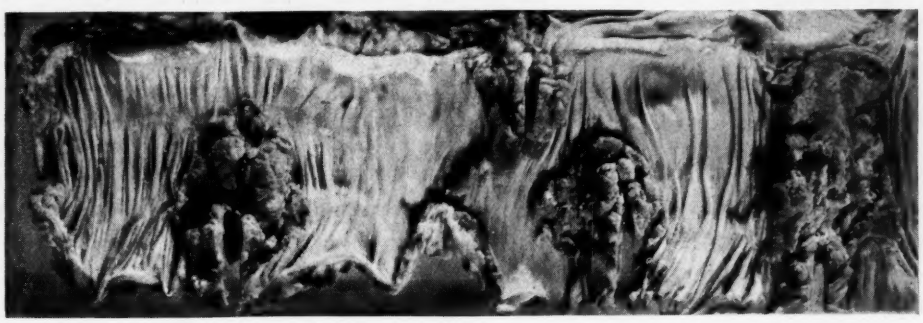

FIG. 378.—*Case* 2. Descending and sigmoid colon, showing four carcinomatous growths. (*St. Mary's Hospital Museum.*)

large growth of pelvic colon, and three smaller growths more proximally (one in iliac colon, two in descending colon). Resection of left colon and anastomosis. Uneventful recovery.

PATHOLOGICAL REPORT.—Examination shows four independent polypoid growths of papillary, alveolar, tubular and trabecular, columnar and spheroidal-celled adenocarcinoma. At least one benign adenomatous polyp is present.

Comment.—This is clearly an example of pluricentric malignant change in a multiple adenomatosis of the colon. The more advanced stage of the distal growth diminishes the likelihood of implantation.

Case 3.—**Carcinoma of pelvic colon. Carcinoma of transverse colon.**

Female, aged 68 (1922). Four months previously cæcostomy (? blind) performed for obstruction. Now obstruction recurred owing to narrowing of cæcostomy. Radiograms show obstruction at junction of iliac and pelvic colon. Operation discovered a fixed malignant mass involving pelvic colon. Left iliac colostomy

attempted, but sigmoid could not be delivered. In attempting transverse colostomy, a second and ring-like growth was discovered in its middle. This was more recent and removable; it was resected and a transverse colostomy established. Patient relieved.

PATHOLOGICAL REPORT.—Ulcerated, alveolar and tubular, columnar-celled, scirrhous carcinoma.

Comment.—The accidental discovery of the second growth in the performance of a colostomy is the outstanding feature. The more advanced condition of the distal growth excludes the chance of implantation, and there is nothing to suggest an origin from preceding adenomatosis.

Case 4.—**Carcinoma of transverse colon. Carcinoma of pelvi-rectal junction. (Author's case.)**

Male, aged 60 (1932). Two months' pain, constipation, and diarrhœa. Radiograms show filling defect in transverse colon and abnormal appearance in lower sigmoid. At operation, freely movable, ring-like growth of transverse colon found. Exploration of pelvis for secondaries revealed a second ring-like growth at pelvi-rectal junction; this was larger and somewhat fixed by recent adhesions. Both the growths resected. Temporary transverse colostomy established at proximal resection and intussusception-anastomosis performed at distal resection. Patient discharged fit, but died from liver metastases nine months later.

Comment.—As in *Case* 3, the second growth was discovered during the exploration necessitated by the first growth. Here, again, the distal growth is the older of the two.

DISCUSSION.

The occurrence of these four cases of multiple cancer of the colon in one surgical firm of this hospital in a period of ten years is surprising in view of the very small number of cases in the literature. Norbury,[13] in his Presidential Address at the Royal Society of Medicine (1930), was able to report only two cases, and to collect three more from the records of three of the larger London hospitals. Lockhart-Mummery,[16] in the discussion which followed, reported five cases of multiple cancer of the alimentary tract, but in none of these was there more than one colonic growth. Abel[17] in 1929 showed three specimens of multiple cancer of the intestine, but only one of these had more than one growth in the colon. Maingot's[18] case presented one growth in the anus, one in the rectum, and only one in the colon.

Bargen and Rankin[14] contribute the largest group of cases in the literature. They mention a case described by Fenger (1888) in which a transverse colostomy was done for a growth at the splenic flexure, with no relief; at autopsy a second growth was found in the ascending colon. They also refer to a case reported by Dowden (1917) in which four metachronous cancers of the colon developed in six years. Finally, they contribute sixteen cases of proved multiple cancer of the intestine, in six of which there were two or more growths in the colon. Three of these six cases are obvious examples of carcinoma supervening on multiple adenomatosis. Case 6 is of great interest: a cancer of the ascending colon was resected in 1920; in 1926 a carcinoma of the sigmoid was resected; in 1929 a third growth was found in the splenic flexure and removed, while in the same year a hysterectomy was done for sarcoma of the uterus!

The accidental discovery of the second growth in two of my cases (*Cases* 3 and 4), and in several cases in the literature, suggests that multiple growths of the colon would be found more frequently if a thorough search were made for them in every case that comes to operation or post-mortem. The clinical importance of such a search is obvious. To overlook a second growth during a resection for operable carcinoma would be a major catastrophe, while colostomy has been performed more than once for inoperable cancer, only to prove a complete failure because a second growth existed higher up. Finally, the possibility of a metachronous growth developing at some future period must influence the prognosis of all operable cancers of the rectum or colon.

Etiology of Multiple Cancer of the Intestine.—When two or more cancers are found in the intestine the first and most obvious explanation is that one is the primary growth and that the others are implantation secondaries. Unfortunately this argument is inadmissible in the great majority of recorded cases, because either the most distal growth is the oldest (e.g., *Cases* 3 and 4 of this series), or the growths are too far apart, or the interval between metachronous growths is too long. Nevertheless, implantation is a possible cause in a few cases (Maingot's case and *Case* 1 of this series).

Pre-existent adenomatous polyposis is a very definite etiological factor. In several published cases (*Case* 2 of this series, Cases 3, 13, and 15 of Bargen and Rankin's series, and others) there is unmistakable evidence, both clinical and pathological, of malignant transformation of preceding adenomata. The majority, however, present no such evidence, and can only be attributed to individual susceptibility, negative immunity, or, of course, coincidence.

By inference, one might argue that a similar etiology operates in single cancers of the colon, except that precancerous adenomatosis is unlikely to play quite as prominent a part.

The association between adenomatous polyposis and carcinoma of the rectum and colon is of obvious importance. Lockhart-Mummery and Cuthbert Dukes[19] consider that this association is frequent, and describe three stages in the transformation: (1) *Stage of hyperplasia*, with irregular epithelial proliferation over extensive areas of the gut; (2) *Stage of polyposis*, with visible sessile and multiple adenomatous polypi; (3) *Stage of malignancy*, one or more of the polypi becoming carcinomatous. They allege that with the development of carcinoma the benign adenomata and hyperplasias retrogress and disappear. If this is true, it would seem that precancerous adenoma might be a common forerunner of cancer of the intestine; in the absence of actual proof, however, this retrogression appears to be somewhat fanciful. Nevertheless, it cannot be denied that there are specimens showing benign adenomata and adenomata undergoing malignant change side by side, and that carcinoma is a potential danger in intestinal polypi.

Actually, three distinct forms of intestinal polypi can be recognized: (1) A familial disorder of young adults, perhaps traceable through several generations, to which the term 'polyposis intestini' has been applied, and which, according to Doering,[20] carries a 60 per cent risk of ultimate carcinoma; (2) The more common and less defined condition known as 'adenomatosis', similar to the above, but without a definite familial or age incidence; (3) The 'pseudo-adenomatous' polypoid hypertrophies and hyperplasias which are seen

in chronic inflammatory lesions of the gut, such as tubercle and bilharziasis. In the present state of our knowledge it is safest to assume that all these types of intestinal polyposis are potentially precancerous, and to act accordingly.

CONCLUSIONS.

1. Multiple primary malignant growths occur more frequently than can be accounted for by coincidence.

2. In some part this may be attributed to the presence of multiple or diffuse precancerous lesions, but a more likely general explanation is an individual susceptibility to malignant disease.

3. One growth does not confer immunity against a second.

4. Multiple carcinoma of the intestine has the same etiology as multiple primary growths elsewhere.

5. Multiple adenoma is a definite cause of multiple cancer of the colon and rectum.

6. All forms of intestinal polypi are potentially malignant and should be treated as such.

7. The possibility that more than one growth may be present or develop should be remembered at all operations for cancer of the intestine, and also in the prognosis.

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SOME EXPERIMENTAL OBSERVATIONS BEARING ON THE ETIOLOGY OF MEGACOLON.

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In the course of an inquiry at the Research Institute of the Cancer Hospital (Free), London, into the part played by irritation in the causation of cancer, the following experiment was performed on eleven young rats: Some powdered crystalline silica was introduced into the mesentery of the cæcum, and a fortnight later intraperitoneal injections of 1 : 2 : 5 : 6-dibenzanthracene were given and thereafter repeated once a week, 1 c.c. of a 0·1 per cent solution of the hydrocarbon in emulsified olive oil being used for each dose. The object was to learn whether a fixation of the carcinogenic agent would result from the chronic inflammation induced by the silica and so cause a tumour to appear in its vicinity.

In one rat only of this series (Rat 8 in *Fig.* 379) did a tumour arise. This rat was killed on account of ascites fifty-three weeks after the injection

FIG. 379.—The vertical lines refer to the duration of life, in weeks, of each rat after the injection of silica into the mesentery of the cæcum. The numbers 1 to 11 at the foot of the vertical lines represent the individual rats. The numbers 10 to 80 at the left-hand side of the figure indicate weeks. All the rats had enlargement of the cæcum at death.

of silica, and was found to have a large solitary spindle-celled tumour in the anterior part of the abdomen, invading the spleen and pancreas. The cæcum and its mesentery were free from growth.

A remarkable feature observed in every one of the eleven rats treated in this way was an enlargement of the cæcum (*Figs.* 380–383). Although this increase in volume of the gut was extensive enough in some of the animals to be detected during life, they appeared to remain in good health.

FIG. 380.—Rat 3, killed thirty-two weeks after the injection of powdered crystalline silica into the mesentery of the cæcum.

The rat with the most pronounced enlargement of the cæcum (No. 5) died thirty-six weeks after the beginning of the experiment and putrefaction prevented a good illustration. The smallest cæcum in this series was found in Rat 9 (*Fig.* 383,A), and in this case the viscus was fixed to the neighbouring structures by extensive adhesions.

Fig. 379 shows the duration of life in weeks of each animal after the introduction of silica into the mesentery of the cæcum.

DISCUSSION.

Admittedly the histological and anatomical study of the cæcal enlargements in these rats has been incomplete, and no control experiments were made. For these reasons the experiment is being repeated. Meanwhile it

FIG. 381.—A, Cæcum of Rat No. 7, fifty-two weeks after the injection of silica into the mesentery of the cæcum; B, Normal rat with cæcum exposed for comparison.

FIG. 382.—Rat 4, killed thirty-two weeks after the injection of silica into the mesentery of the cæcum.

may be justifiable to consider the cause of the enlargements. The first suggestion is that they might have been the consequence of some obstruction of the bowel either by adhesions or by a torsion of the mesentery. No clear evidence is visible of such blockage, and the rats did not appear to suffer from ill health, nor did they eventually die from intestinal obstruction.

The most plausible explanation seems to be that the enlargement has resulted from an overaction of the sympathetic nerves as a consequence of the continued irritation produced by the powdered silica—an irritation to

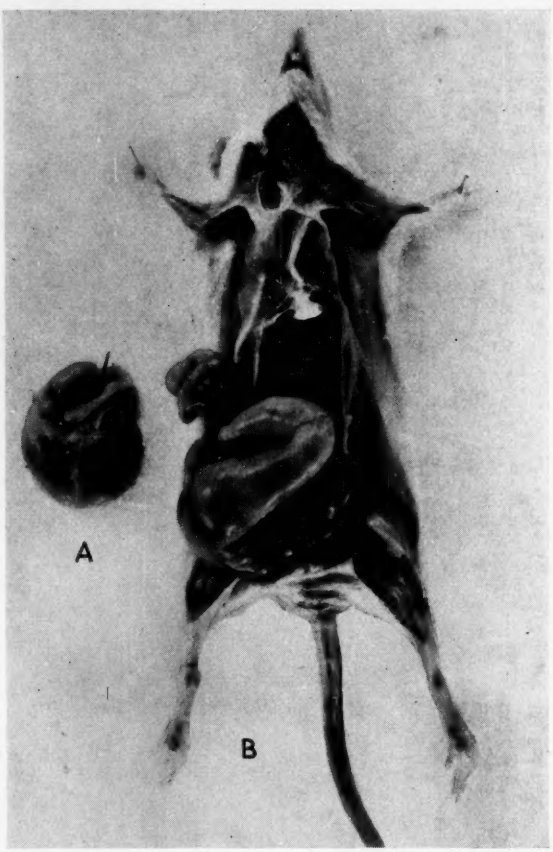

FIG. 383.—A, Cæcum of Rat 9, fifty-six weeks after the injection of silica into the mesentery; B, Rat 6, forty weeks after the injection of silica.

which the parasympathetic nerve-supply presumably would not be exposed owing to its different anatomical relationships. The function of the sympathetic nerves is said to be a stimulation of the circular muscle fibres of the sphincters; while this stimulation continues the action of the parasympathetic nerves, which supply the other muscle fibres of the gut, is inhibited. The modern operation of ramisectomy and sympathectomy as introduced by Wade and Royle[1] for the cure of megacolon puts the responsible overactive sympathetic nerves out of action, leaving the parasympathetic system intact.

Powdered crystalline silica is a persistent irritant when lying in the tissues; and if the current hypothesis which attributes megacolon to overaction of the sympathetic nerve-supply of the segment of bowel concerned is true, then it would not be surprising if the condition could be produced in animals experimentally by causing chronic irritation of the appropriate sympathetic nerves.

The cæcal enlargement in rats reported in the present paper followed quickly after the injection of silica, and in one animal (No. 5) was observed during life, although not especially sought or expected, within fourteen days.

SUMMARY.

Enlargement of the cæcum following injections of crystalline silica into the mesentery of the cæcum is recorded as occurring in rats. A possible bearing of this observation on the etiology of megacolon is suggested.

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THE PATHOLOGY OF ACUTE STRANGULATION OF THE INTESTINE.

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INTRODUCTION.

It is rather surprising that such a common clinical condition as acute strangulation should have received so little attention from the innumerable workers who have attempted to solve the complicated problem provided by the group of conditions which fall under the general heading of acute intestinal obstruction. Acute strangulation has long been differentiated clinically from simple intestinal obstruction, and, whilst this difference has been recognized by many experimental workers,[1-7] only a few of them have dealt with experimentally produced strangulation. The cause of death has usually been considered to be a toxæmia resulting from the absorption of toxic substances produced in the strangulated segment of bowel. This view was derived from the bulk of experimental evidence then available, for it had been shown that the intestinal content of a strangulated loop when injected, preferably intravenously, into another animal caused the rapid death of that animal. Among the earlier workers Von Albeck[8] considered that death was due to the absorption of putrefactive toxins formed in the strangulated loop, whilst Murphy and Vincent[4] believed that the symptoms and death were due to a 'bacterial endotoxæmia'. Eisberg[9] was one of the few workers who did not completely accept the general view of the cause of death, and suggested that death sometimes took place long before there had been time for bacterial action to play a part in the result. All were agreed that strangulation was a more acute condition than simple obstruction and that death took place more rapidly in the former condition.

The blood chemistry of acute strangulation has been studied by many workers, and their findings are in general agreement. Death takes place so rapidly that dehydration from vomiting does not occur and the changes in the chemistry of the blood and urine are not marked. Copher and Brooks[11] have reported death in acute strangulation without blood changes, but there is usually a rise in the blood-urea. Foster and Hausler[10] concluded from their investigations that whilst dehydration, hypochloræmia, and alkalosis were not present to any appreciable degree there was a moderate increase in the urea and non-protein nitrogen. This increase was evidently due to retention, since nearly all animals dying from strangulation have an almost complete anuria. As might be expected from such blood findings, the administration of sodium chloride solutions does little good in acute strangulation.

The term 'strangulation' implies an interference with the blood-supply, and it is evident that this interference may affect the arteries alone, the veins

alone, or both arteries and veins simultaneously. Only the latter two conditions require consideration in strangulation obstruction where the mechanism which causes an obstruction of the bowel also affects the blood-supply.

Vincent and Murphy[4] first called attention to the early onset of intoxication in cases of acute obstruction accompanied by a venous obstruction. But it was not until 1924, when Foster and Hausler[10] published their work on acute strangulation, that further light was thrown on this subject. These two workers carried out a most interesting series of experiments. They first tied off varying lengths of bowel in such a way as to cause a complete venous obstruction, and records of the temperature, pulse-rate, respiration-rate, and blood-pressure were taken at definite intervals. They found that their results varied with the length of bowel affected. In cases with long segments the blood-pressure fell rapidly, the pulse-rate increased very markedly, the temperature fell, and the animal died from shock before toxæmia could develop. With the shorter segments the fall in blood-pressure was only moderate, the pulse-rate was not extremely rapid, and the animals overcame the primary shock only to succumb later to a terrific toxæmia and peritonitis. The differences between long and short loops were brought out more clearly when they repeated the above experiments enclosing the strangulated loop in a thin rubber bag which prevented the absorption of toxins via the peritoneum from the strangulated segments. They found that in the long-segment group the use of a rubber bag did not affect the outcome, whilst in the short-segment group the length of life was markedly lengthened. Later experiments were carried out in which the intestine was tied so tightly that a complete and instantaneous anæmia was produced. This group presented an entirely different picture. There were none of the symptoms of acute collapse so evident in the venous obstruction series. Instead they found a slight gradual rise in the pulse-rate and a practically normal blood-pressure during the first fifteen hours. The onset of peritonitis was then indicated by a rapid rise in the temperature and respiration-rate.

It was evident from these experiments that the cause of death in cases of acute strangulation in which venous obstruction alone exists differs from similar cases in which both arteries and veins were occluded. It is possible, therefore, to divide cases of experimental strangulation into two groups: (1) Those cases in which venous obstruction alone is produced; (2) Those cases in which both arteries and veins are tied. This grouping will be used in this paper to simplify the account of the experiments performed by the writer. It is also preferable to subdivide the venous-obstruction group according to the length of bowel strangulated. Foster and Hausler,[10] in commenting on their results, stated that: (1) In long loops the predominant lethal factor is shock; and (2) In shorter loops shock, although present, is not of sufficient intensity to cause death, and time is allowed for toxæmia and peritonitis to develop.

OBJECTS OF THIS PAPER.

It appeared impossible to the writer to obtain a clear and detailed explanation of the pathology of acute strangulation in spite of the excellent experimental work already published. After a careful study of the literature

the following problems were selected for solution : (1) The cause of the circulatory collapse in venous strangulation of long loops of intestine ; (2) Is the absorption of toxic substances from a strangulated loop the cause of death when the loop is only of moderate length ? (3) What is the route of absorption of such toxins and their mode of production ? (4) An explanation of the cause of death when very short loops of gut are strangulated.

The experiments reported in this paper were carried out in an effort to clear up these remaining problems. In all cases dogs were used for the experimental work and every effort was made to prevent any unnecessary pain or discomfort to the animals. All abdominal operations were done under ether anæsthesia preceded by an injection of morphia, and a full aseptic technique was maintained throughout. The blood-pressure readings were carried out by means of a small cannula inserted into the femoral artery through an incision made at the time of the abdominal operation, and it was found that repeated readings could be obtained without loss of blood or discomfort to the animal. At the outset it was realized that, in order to obtain reliable results, the strangulation of the loop must be carefully produced. The encircling ligature used by many of the earlier workers was not employed. The closed loop was produced by using separate tape ligatures obstructing the length of bowel required, and strangulation was produced by dissecting out the vessels in the mesentery and tying them separately with fine silk ligatures.

THE PATHOLOGY OF ACUTE STRANGULATION OF THE INTESTINE IN WHICH VENOUS OBSTRUCTION ALONE EXISTS.

The results of the work already published on this problem may be summarized briefly as follows : Death in acute strangulation is due to a varying combination of shock and toxæmia, and the preponderance of one or other of these factors is determined by the length of bowel involved and the degree of venous occlusion produced. For the purposes of this paper the experiments and results are divided into three groups according to the length of bowel involved in the strangulation. The groups are : (*I*) *Strangulation of long loops of intestine, 40 cm. or more ;* (*II*) *Strangulation of moderate-sized loops, 20 to 40 cm. ;* (*III*) *Strangulation of short loops, less than 20 cm.* This subdivision has been adopted because the results suggest that a different factor is the main cause of death in each of the three groups.

I. STRANGULATION OF LONG LOOPS OF SMALL INTESTINE

The experiments of Foster and Hausler[10] have already been mentioned in which they charted the changes in the blood-pressure, pulse-rate, etc., which take place in animals with strangulation of long loops of intestine. When their results were charted it was found that a rapid and steady fall in the systolic blood-pressure from an average of 150 mm. of mercury to 40 mm., and a rise in the pulse-rate from about 80 or 90 beats per minute to about 240, took place and that death occurred soon after these figures were reached. They concluded that shock was the main lethal factor in these cases and suggested that the shock was due to a combination of the pain resulting from

the twisting of the mesentery, the inactivity of the ductless glands, and the hæmorrhage into the loop. The first object of the experimental work to be reported was an investigation into the exact cause of the shock which is so marked a feature in these cases.

1. The Cause of the Circulatory Collapse Associated with Strangulation of Long Loops of Intestine.—It is not the intention of the writer in this paper to enter into a discussion on the merits of the numerous explanations of the circulatory collapse which is commonly known as shock. The work of Blalock and his associates,[12] showing that the symptoms of collapse in traumatic shock are due to the withdrawal of large quantities of blood or blood-plasma from the circulation into the traumatized area, provides the most reasonable theory so far produced. They studied the effects of the rapid loss of blood and reported that recovery was problematical if the loss exceeded an amount equal to 50 per cent of the blood volume or 4 per cent of the body weight. The significance of these results is readily appreciated when the changes taking place in an obstructed loop of intestine, after the ligation of its veins, are considered. The course of events in such a strangulated loop has been well described by McIver and White.[13] They reported the changes as follows: "The colour of the strangulated loop changes immediately to a dusky red, soon turns a dark red, and finally becomes black. At the same time intense tonic contractions of the whole loop or isolated segments take place and these contractions continue for several hours. Distension of the loop takes place shortly after the obstruction is produced and the thick red exudate found in the lumen is composed largely of blood cells and serum. The peritoneal coat remains smooth and glistening and only in those cases where strangulation has existed about twenty-four hours is a thin coating of fibrin found on the surface. The loop increases in length sometimes as much as three times its original length, and the corresponding changes take place in its diameter. Sections of the bowel wall show a considerable disintegration of the normal structure, the tissue spaces are filled with red blood cells and the mucosa is almost completely degenerated." The appearance of such a loop suggests that it contains an excessive quantity of blood which is being withheld from the circulation. The following experiment from the author's series illustrates the circulatory changes taking place.

Experiment I.—Adult dog. Weight 13½ kilos.

11.0 a.m. ¼ gr. morphine.

11.30 a.m. Operation. Ether anæsthesia. A loop of small intestine about 100 cm. in length obstructed by tape ligatures. The veins draining the loop were dissected out in the mesentery and ligated with fine silk. The anastomotic channel along the mesenteric border of the intestine was also ligated with silk.

	B.P.	P.
	150	90
12.30 p.m.	135	135
1.30 p.m.	110	170
3.10 p.m.	45	240

When the last reading was made the dog was unconscious and moribund. Death occurred shortly afterwards and an immediate autopsy was performed. The strangulated loop was found unperforated, very distended, and its walls much

thickened. The loop was removed intact and weighed. It was estimated to have gained in weight the astonishing amount of 570 grm., which was equivalent to 4·5 per cent of the body weight or to more than 50 per cent of the blood volume.

Further experiments showed that loops of intestine treated in the same manner were capable of gaining weight in the proportion of 125 to 150 grm. per 25 cm. length. When the gross and microscopic appearance of a strangulated loop is considered it is at once evident that this gain in weight represents the amount of blood which has been withdrawn from the circulation. As corroborative evidence McIver and White[13] reported a considerable decrease in the blood volume of cats dying from acute strangulation. In the above experiment more than 50 per cent of the total blood volume was removed from the circulation in the space of about four hours by the strangulated loop, and the blood-pressure and pulse readings testify to its effect on the circulation. It is evident, therefore, that in venous strangulation of long loops of intestine (40 cm. or more in a dog of average weight) blood may be rapidly withheld from the circulation in sufficient quantity to cause death.

2. **The Relation of Toxæmia to the Cause of Death in Strangulation of Long Loops.**—The theory that death in acute strangulation is always associated with the absorption of toxic substances from the strangulated loop is a view which is still widely held. Eisberg[9] was one of the earlier workers on the subject who suggested that death sometimes occurred so rapidly that it was doubtful whether there had been time for bacterial action to produce toxins in sufficient quantity to cause death. The first direct evidence on the subject was produced by Foster and Hausler.[10] They enclosed the strangulated loop in a rubber bag in such a way that absorption from the loop by the peritoneal serosa was prevented without interfering with the distension of the segment by blood and gas. When long loops were strangulated their experiments showed that life was not prolonged by this procedure. Furthermore, they were unable to demonstrate that the fluids which accumulate in the peritoneal cavity or in the lumen of a strangulated loop of less than twelve hours' duration possess any marked toxic properties when injected intraperitoneally into other dogs, even in massive doses. The results were confirmed by the writer. Whilst repeating these experiments of Foster's large quantities of the fluid exuding from such long loops were collected in rubber bags by the writer. Intravenous injection of large quantities of this exudate (as much as 200 c.c. in one dog) produced nothing more serious than a transient weakness and tremor of the limbs accompanied by salivation and vomiting. (It is interesting to note that intraperitoneal injection of this fluid into guinea-pigs frequently produced death with all the symptoms of histamine poisoning. This illustrates well the danger of utilizing different species of animals for such injection experiments.) It is evident from these experiments that toxæmia is of little if any importance in causing the death of animals with strangulation of long loops of intestine.

3. **Conclusion.**—Evidence has been brought forward to show that the symptoms of circulatory collapse associated with an acute strangulation of a long loop of intestine is due to the rapid withdrawal of a large amount of blood from the circulation by the loop—a conclusion also reached by Scott and Wangensteen.[15] Toxæmia has been shown to be of minor importance

in this group of cases, and, in the author's opinion, the cause of death is the acute reduction of the circulating blood volume.

II. STRANGULATION OF LOOPS OF MODERATE LENGTH.

1. **Circulatory Changes.**—The withdrawal of blood from the circulation by a strangulated loop of intestine does not continue indefinitely. The loss is most rapid in the first few hours after strangulation is produced, but is then progressively limited by the thrombosis which, beginning in the veins and capillaries, finally spreads to the smaller arteries. It is evident, therefore, that medium and short loops when strangulated are unable to cause death in the same manner as long loops of gut. Foster and Hausler[10] added considerably to the solution of this problem. They studied the circulatory changes taking place when medium-sized lengths of gut (15 to 25 cm.) were strangulated. They found that the blood-pressure fell in the first six hours to approximately 110 mm. systolic and remained at this level until several hours before death. This stationary period was followed by a very rapid fall, often amounting to 60 mm. in an hour's time. The pulse-rate showed a corresponding rise within the first six hours to an average of 140 beats per minute. After about sixteen hours the rate rose to about 200 and continued at or about that level until death. The following experiments from the writer's series are good illustrations of the circulatory changes :—

Experiment II.—Bitch. Weight 10 kilos.
3.30 p.m. B.P. 145. P. 90.
Operation. ¼ gr. morphine and ether anæsthesia. A 25-cm. loop of jejunum obstructed with tape ligatures. Veins draining the loop dissected in mesentery and tied with silk ligatures.

	B.P.	P.
11.0 p.m.	110	160
11.30 a.m.	105	220
2.0 p.m.	105	220
5.0 p.m.	100	240
7.0 p.m.	Dead.	

An immediate autopsy showed the loop distended and not perforated. There was a fair quantity of dark fluid in the peritoneum, but no macroscopic evidence of peritonitis.

Experiment III.—Bitch. Weight 9 kilos.
2.30 p.m. Operation. ¼ gr. morphine and ether anæsthesia. Loop of small intestine 25 cm. long, about 45 cm. below Treitz ligament, obstructed and veins ligated. At conclusion :—

	B.P.	P.	
	135	90	
9.30 p.m.	120	170	
11.30 a.m.	120	190	
1.30 p.m.	115	240	
4.30 p.m.	60	300	
7.0 p.m.	Dead.		Autopsy showed loop intact.

The initial fall in blood-pressure is easily explained by the loss of blood into the loop, and the stationary period corresponds to the stage when

thrombosis has become well marked. The terminal fall in pressure requires explanation. Foster and Hausler[10] repeated these experiments, enclosing the loop in a rubber bag. They found that they were able to prolong the lives of the animals for several days. They therefore concluded that the terminal fall in blood-pressure was due to the onset of toxæmia and peritonitis. Chenut,[14] in his experiments, showed that life could be prolonged in cases of strangulation if the strangulated loop were sutured outside the abdominal cavity. He found that the loop sloughed away and the animals died of the resulting fistula. The following experiment from the author's series is quite in keeping with Chenut's results.

Experiment IV.—This was a repetition of Foster and Hausler's experiment of enclosing the strangulated loop in a rubber bag with the addition that the rubber bag was drained on to the surface of the body. This was found to be necessary because in a few earlier experiments fluid collected in the rubber bag in such quantity as to force its way past the ligature holding the bag over the loop. Previously a lateral anastomosis between the bowel proximal and distal to the loop to be strangulated was performed.

Feb. 5, 1932.—Morphine and ether anæsthesia. Preliminary lateral anastomosis performed.

March 2.—$\frac{1}{4}$ gr. morphine half an hour before operation. Ether anæsthesia. A 20-cm. loop of small intestine obstructed and its veins ligated. The loop was enclosed in a rubber bag and sutured extraperitoneally. Later in the day 40 c.c. blood-tinged, odourless fluid removed from the bag.

March 3.—Animal well and walking around cage; 80 c.c. fluid, almost black, light foul odour, removed from rubber bag. Tube stitched into rubber bag drainng on the surface of the abdominal wall.

March 9.—Dog perfectly well. Utilized later for other experiment.

The lateral anastomosis was performed so that the picture should not be complicated by a small-gut obstruction, which in itself is liable to be fatal in an experiment of more than a few days' duration. This dog was perfectly well eight days after the experiment. It is evident that life in these cases is prolonged if absorption of substances from the strangulated loop is prevented. It appears, therefore, that the terminal fall of blood-pressure which occurs in the strangulation of intestinal loops of moderate length is due to the absorption of substances from the loop.

2. Evidence to Show that Toxic Substances are Present in the Fluid Exuding from a Strangulated Loop.—Absorption of substances from a strangulated loop is possible by two paths, the lymphatic channels or the peritoneal cavity. It has been found by experiment that the result is not altered by ligating the lymphatics in the mesentery, and it is generally conceded that absorption takes place via the peritoneal cavity. Whilst there is no doubt of the toxicity of the loop contents of these dogs dying of intestinal strangulation, all attempts to prove the presence of a toxin in the peritoneal fluid in such cases have been unsuccessful. Scott and Wangensteen[16] concluded that the peritoneal fluid obtained from dogs dying of acute strangulation is non-toxic when injected intravenously into normal dogs, providing the strangulated loop is not ruptured or about to rupture and the fluid does not give off a foul odour. Wilkie[7] obtained similar results, but added that "these negative findings only prove that there is insufficient toxin in the

peritoneal fluid at the time of death and does not preclude a steady continuous absorption, the cumulative effect of which is sufficient to produce toxæmia and death". That toxic substances are present in the exudate from a strangulated loop is proved by the following experiment of the writer's :—

Experiment V.—Bitch. Weight 10 kilos.
2.30 p.m. Operation. Loop of jejunum 25 cm. long and about 30 cm. below Treitz ligament obstructed. Loop enclosed in rubber bag draining on to the surface of abdomen. At conclusion of experiment :—
B.P. 125. P. 160.
11.20 a.m. B.P. 120. P. 180.
Contents of rubber bag removed and re-injected intraperitoneally.
1.0 p.m. B.P. 105. P. 200.
2.30 p.m. B.P. 30. P. not countable.
2.35 p.m. Dead. Immediate autopsy. Loop had not perforated.

In this experiment all the fluid exuding from outside the loop during the first twenty-one hours of strangulation was collected by the rubber bag and was not diluted by the addition of any peritoneal fluid. It was injected intraperitoneally to utilize as far as possible the normal route of absorption. Its effect is shown by the blood-pressure and pulse records, death occurring about three hours after the injection. An immediate autopsy was performed and the strangulated loop was found to be intact so that it was clear that the exudate had not been contaminated by any substances resulting from a rupture of the loop. It has, however, been shown that the fluid exuding from strangulated loops within the first twelve hours after onset is non-toxic.[10] Experiments were carried out by the writer in order to find out if possible the time at which the exudate begins to contain toxic substances. The following is a typical example of the results obtained :—

Experiment VI.—Dog. A loop of jejunum 25 cm. in length obstructed and its veins ligated. Loop enclosed in a rubber bag into which a tube was inserted draining to surface of abdomen.
2.0 p.m. Operation. $\frac{1}{4}$ gr. morphine and ether anæsthesia.
4.30 p.m. B.P. 120. P. 140.
10.30 p.m. B.P. 100. P. 160.
90 c.c. fluid, odourless, slightly blood-stained, coagulating on standing, removed from bag. 70 c.c. injected intraperitoneally.
10.30 a.m. B.P. 90. P. 150.
100 c.c. removed from rubber bag, fluid now darker in colour, slight odour.
3.0 p.m. B.P. 90. P. 180.
60 c.c. dark coloured fluid removed. Odour more pronounced. 50 c.c. re-injected.
3.30 p.m. B.P. 50. P. 240.
4.15 p.m. Dead. Autopsy showed loop of gut was not perforated.

In this experiment it was possible to remove at intervals the fluid exuding from the loop which collected in the rubber bag. The major portion of the fluid removed was promptly re-injected intraperitoneally and the effect on the blood-pressure and pulse-rate observed. It is noticeable that the earlier injections had very little effect—in fact, the animal's condition showed little alteration in the period between eight and twenty-three hours after the onset of strangulation. But the effect of the injection of the fluid which exuded from the gut between the twentieth and twenty-third hours of

strangulation was prompt and marked, the blood-pressure falling within half an hour and death ensuing one and one quarter hours after the injection. These results were confirmed over a series of cases. It is important to note that the loops were found intact at autopsy; in fact, if the loop strangulated is more than 15 cm. in length, death usually takes place before perforation of the gut occurs. It can be concluded, therefore, that there are present in the fluid exuding from a strangulated loop substances which on absorption from the peritoneum cause death. These substances are not present in the exudate in the early stages, but begin to appear probably about sixteen to twenty hours after the onset and are soon present in sufficient amount to cause death.

3. The Origin of the Toxic Substances Present in the Exudate.—The mode of production of the toxins of acute obstruction has been adequately dealt with by other authors. After a prolonged controversy it is now generally believed that the toxins are the direct result of bacterial action. Dragstedt and his co-workers[17] succeeded in sterilizing short loops of intestine by allowing them to drain freely into the peritoneal cavity, and found that such sterile loops could be strangulated without causing the death of the animal. Murphy and Brooks[18] did the same experiments with similar results and took this to be the final proof that bacteria elaborated the toxin. This view is now held by the majority of investigators. But the object of this section is to discuss the means by which the toxic substances pass from the strangulated loop into the fluid exuding from the loop. It is well known that the lumen contents of a strangulated loop become increasingly toxic after about sixteen hours from the onset of strangulation. It would appear that the lumen contents are therefore the obvious origin of the toxic substances which are found in the exudate and in order to leave the loop in the exudate the toxins must permeate the wall of the intestine. The early exudate from the loop is an odourless, strawberry-coloured fluid which coagulates on standing and is practically indistinguishable from blood-plasma. After about sixteen hours the fluid is found to become darker in colour, later almost black, to be no longer spontaneously coagulable, and to have acquired a faint but definite trace of the odour characteristic of the contents of a strangulated loop. This suggested that after about twenty hours the wall of the intestine was becoming permeable to the loop contents. The permeability of the intestinal wall was investigated by the following experiments:—

Experiment VII.—An enterostomy was performed in such a fashion that whilst one end of the catheter came out on to the abdominal wall the other end passed into the segment of gut to be strangulated. Strangulation was produced by ligating the veins in the mesentery and by including the anastomosing channels at the mesenteric attachment of the bowel within the ligatures which occluded the intestine. The strangulated loop was then enclosed in a rubber bag into the apex of which a rubber tube was fastened and brought out to the abdominal wall. By these means it was possible to obtain samples of the contents of the bowel lumen and of the fluid exuding from the gut simultaneously. At the same time it was possible to measure the pressure within the strangulated loop. In order to have a means of comparing the respective compositions of the fluid exuding from the gut and of the lumen contents the samples were estimated for chloride, sugar, and non-protein nitrogen content. The following tables indicate the results:—

	Plasma			Exudate			Gut Contents		
	N.P.N.	Sugar	Cl	N.P.N.	Sugar	Cl	N.P.N.	Sugar	Cl
Operation 1.									
5 hrs. later ..	39	108	478	31	86	632	31	30	548
12 hrs. later ..	—	—	—	29	43	640	39	10	528
24 hrs. later ..	43	96	432	56	10	610	82	8	454
Operation 2.									
4 hrs. later ..	23	139	435	25	80	596	32	30	495
11 hrs. later ..	—	—	—	21	26	566	36	19	484
23 hrs. later ..	27	—	—	34	16	508	62	7	474
Operation 3.									
At operation ..	26	178	458	—	—	—	—	—	—
4 hrs. later ..	30	121	408	23	101	622	36	42	532
20 hrs. later ..	36	72	384	34	14	596	49	8	496
Operation 4. ..									
At operation ..	23	240	514	—	—	—	—	—	—
8 hrs. later ..	17	—	—	26	58	574	69	10	524
20 hrs. later ..	24	234	462	124	12	572	284	9	460
Operation 5.									
At operation ..	22	181	508	—	—	—	—	—	—
8 hrs. later ..	27	197	460	23	87	632	44	13	504
20 hrs. later ..	33	94	450	32	15	614	92	10	502
22 hrs. later ..	—	—	—	38	15	586	106	8	502
Operation 6.									
8 hrs. later ..	—	—	—	24	—	—	58	—	—
20 hrs. later ..	—	—	—	47	—	—	—	—	—
22 hrs. later ..	—	—	—	48	—	—	132	—	—
24 hrs. later ..	—	—	—	55	—	—	—	—	—
26 hrs. later ..	—	—	—	60	—	—	118	—	—

A superficial glance at these results might suggest that the composition of the exudate from the gut follows that of the loop contents. The chlorides remain steady or show a slight fall. The sugar estimation falls in both cases, earlier in the case of the loop contents, probably as a result of bacterial action. More interest centres around the non-protein nitrogen. Whilst a steady rise takes place in the non-protein nitrogen of the loop contents, little change is found in the fluid outside the loop until after the expiration of about twenty hours, at about which time a definite rise in the non-protein nitrogen is noticeable. But even after the expiration of twenty hours the composition of the fluid exuding from the loop is not the same as that in the lumen of the intestine as shown by Operations 5 and 6 in the above group. At the same time an investigation into the pressure existing within the lumen of strangulated loops was carried out. The pressure was very quickly found to rise to between 45 and 75 cm. water. This pressure was maintained for about fifteen to twenty hours and was then found to fall slowly. If the blood-pressure readings are recalled with the sudden and fatal fall occurring about twenty to twenty-four hours after the onset, it would appear that, at this stage, when the lumen pressure is also falling, the wall of the intestine becomes permeable to the toxic substances present in the loop content. This view was held by the writer until the following experiments convinced him that the explanation was not necessarily such a simple one.

Experiment VIII A (May 4, 1932).—Dog. Weight 12 kilos.

3.0 p.m. Operation. ¼ gr. morphine and ether anæsthesia. A loop of jejunum 20 cm. long obstructed and its veins ligated. Catheter sutured into loops.

	B.P.	Pulse	Lumen Pressure cm. H_2O	Lumen Contents Fluid	Gas
11.0 p.m. ..	—	—	59	55 c.c.	2 c.c.
11.0 a.m. ..	110	160	47	50 c.c.	18 c.c.
3.0 p.m. ..	112	180	26	47 c.c.	18 c.c.
6.30 p.m. ..	115	220	27	47 c.c.	18 c.c.
10.0 p.m. ..	115	220	27	47 c.c.	18 c.c.

Midnight. Dead. Loop intact.

Experiment VIII B (April 11, 1932).—Bitch. Weight 10 kilos.

3.30 p.m. Operation. 25 cm. loop of jejunum obstructed and veins ligated. Catheter sutured into loop.

	B.P.	Pulse	Lumen Pressure cm. H_2O	Lumen Contents Fluid	Gas
3.30 p.m. ..	135	90	—	—	—
11.0 p.m. ..	110	160	36	45 c.c.	—
11.0 a.m. ..	105	220	45	75 c.c.	25 c.c.
2.0 p.m. ..	105	220	40	70 c.c.	30 c.c.
5.0 p.m. ..	100	240	30	65 c.c.	35 c.c.

7.0 p.m. Dead. Loop intact.

Experiment VIII C (May 4, 1932).—Bitch. Weight 10 kilos.

3.45 p.m. Operation. ¼ gr. morphine and ether anæsthesia. Veins to a loop of small intestine 25 cm. long ligated. Loop obstructed and catheter sutured into loop in manner previously described. Blood-pressure readings obtained from femoral artery.

	B.P.	Pulse	Lumen Pressure cm. H_2O	Lumen Contents Fluid	Gas
11.0 p.m. ..	120	160	29	20 c.c.	8 c.c.
12.0 noon ..	112	200	43	15 c.c.	20 c.c.
3.15 p.m. ..	110	240	29	15 c.c.	20 c.c.
7.0 p.m. ..	85	240	30	8 c.c.	22 c.c.

10.0 p.m. Dead. Autopsy showed the loop only slightly distended but not perforated.

Experiment VIII D (April 11, 1932).—Dog. Weight 10 kilos.

2.30 p.m. Operation. ¼ gr. morphine and ether anæsthesia. Loop of jejunum 25 cm. long about 30 cm. below Treitz ligament obstructed and veins ligated. Catheter sutured into loop which was enclosed in a rubber bag draining by a tube on to the surface.

	B.P.	Pulse	Lumen Pressure cm. H_2O	Lumen Contents Fluid	Gas
4.30 p.m. ..	—	—	70	25 c.c.	—
10.0 p.m. ..	140	60	70	25 c.c.	10 c.c.
11.30 a.m. ..	130	160	70	15 c.c.	40 c.c.
12.0 noon ..	125	160	70	10 c.c.	40 c.c.
2.30 p.m. ..	110	170	65	12 c.c.	43 c.c.
4.15 p.m. ..	95	190	47	12 c.c.	43 c.c.

4.35 p.m. Dead. Autopsy again showed an intact loop.

The first point to be considered in the above experiments is the pressure registered in the lumen. Fluid is poured into the lumen of the loop shortly after strangulation is produced, and the volume apparently reaches its

maximum about eight to twelve hours after the onset, and some time later, about twenty hours after the onset, there appears to be a tendency for the fluid to leave the lumen. It would seem that the early pressures are independent of the volume of the loop contents and probably are indicative of the tonic contractions which are known to take place after strangulation has been produced and to last for several hours.[13] But as the pressure falls there is no corresponding reduction in the volume of the loop contents—in fact, there appears to be an increase in the volume of the loop contents owing to the production of gas taking place at the very time when the loop pressure is falling. In none of the above experiments could it be shown that any considerable volume of fluid passed out of the lumen before death took place.

Various experiments were carried out in which substances easily recognizable by colour reactions such as phenolsulphonephthalein and potassium ferricyanide were introduced into the lumen of the loop at the time of strangulation. The presence of these substances was never demonstrable in the exudate from the loop, but at the time this failure was attributed to technical difficulties associated with the high protein content of the exudate. The experiments have more significance when considered with the convincing results published by Scott and Wangensteen on the absorption of strychnine sulphate from strangulated loops of intestine.[19] They were unable to show that strychnine passed out of strangulated loops in the absence of perforation of the intestinal wall. But it must be noted that in their experiments such long loops of gut were used that death followed in about eight to ten hours.

In an attack on the problem from another angle the following experiments were performed in which the contents of the lumen were removed at intervals and replaced by a corresponding volume of air or water.

Experiment IX A (May 16, 1932).—Bitch. Weight 9 kilos.

10.15 p.m.	Operation. ¼ gr. morphine and ether anæsthesia. Loop of jejunum 25 cm. long obstructed and veins ligated. Catheter sutured into loop.
Noon.	Following day. Contents removed and, after the loop had been washed out several times with water, they were replaced by 60 c.c. air.
	B.P. 105. Pulse 200. Lumen pressure 50 cm.
4.30 p.m.	Loop found to contain 55 c.c. gas and 10 c.c. fluid. Replaced by equal volume air after washing of loop.
	B.P. 100. Pulse 240. Lumen pressure 53 cm.
11.0 p.m.	Loop found to contain 67 c.c. gas and 3 c.c. of fluid. Loop washed and 70 c.c. air injected.
	B.P. 95. Pulse 240. Lumen pressure 50 cm.
6.30 a.m.	Dead. Autopsy showed loop intact.

Experiment IX B (May 24, 1932).—Dog. Weight 9 kilos.

10.30 p.m.	Operation. About 25 cm. ileum obstructed and veins ligated. Catheter sutured into loop.
11.0 p.m.	Loop found to contain 16 c.c. fluid and 44 c.c. gas. Replaced by same volume air.
3.0 p.m.	Loop found to contain 62 c.c. gas and 3 c.c. fluid. Replaced by water.
11.0 p.m.	Dog very sick.
8.0 a.m.	Found dead. Cold and evidently been dead for several hours. Loop not perforated.

Experiment IX C (June 7, 1932).—Dog. Weight 9 kilos.

10.30 a.m.	Operation. Loop of ileum 20 cm. long obstructed and veins ligated. Catheter sutured into loop.
10.30 p.m.	28 c.c. of fluid removed from loop and replaced by air.
10.30 a.m.	Contents replaced by water.
10.30 p.m.	Dog very sick.
8.0 a.m.	Found dead. Cold and evidently dead several hours.

Six of these experiments were carried out, and in none of them could it be shown that life had been prolonged as a result of the removal of the loop contents. Furthermore, a comparison of the amount of fluid exuding from a strangulated loop and the volume of fluid in the lumen brings out the following figures :—

Experiment X A.—

Hours Strangulated	Total Volume of Exudate c.c.	Volume of Loop Contents Gas	Fluid
2	10	—	25
8	36	10	25
20	160	40	15
22	190	40	10
24	208	43	12
26	223	43	12

Experiment X B.—

8	35	—	45
20	100	25	75
22	135	30	70
24	160	—	—
26	175	35	65

The large volume of fluid exuding from a strangulated loop during twenty-four hours is well shown in the above figures. During the period between the eighth and twenty-sixth hour of strangulation 188 c.c. were exuding from the loop whilst 13 c.c. were passing from the lumen in the first experiment. Corresponding figures for the second experiment are 140 and 10. In the writer's experience the lumen content of a loop strangulated for twenty four hours has not been sufficiently highly toxic to cause death when reaching the peritoneum in such small amounts over such a period. It would appear, therefore, that the toxic substances shown to be present in the exudate from the loop are not derived mainly from the loop contents. They must, therefore, be formed in the wall of the intestine.

4. **Conclusion.**—When a loop of intestine of moderate length (20 to to 40 cm. in the average dog) is strangulated insufficient blood is withdrawn from the circulation to cause death. The animal lives long enough for the intestinal bacteria to invade the tissues of the intestinal wall and produce toxic substances which pass out of the strangulated loop into the peritoneal cavity and when absorbed cause death. These toxins are present in the exudate from the strangulated loop in increasing amounts after about sixteen hours from the onset of strangulation. The toxins in the exudate are produced in the wall of the intestine and do not result from the permeation of the intestinal wall by the toxic substances present in the contents of the the intestinal lumen.

III. THE STRANGULATION OF SHORT LOOPS.

The strangulation of short loops of intestine provides still another problem. The withdrawal of blood from the circulation into the loop is small and the amount of toxin present in the exudate from the loop is insufficient to cause death rapidly. As a result the disintegration of the intestinal wall progresses until perforation takes place and the contents of the lumen escape into the peritoneal cavity. The absorption of the additional toxin from the lumen contents may be sufficient to cause death soon after the loop perforates. If not, the animal develops a widespread peritonitis from which death quickly ensues. There still remains for investigation the group of cases in which only a knuckle of gut is strangulated. With these very small loops interesting results are obtained :—

Experiment 1 (April 25, 1932).—Bitch. Weight 10 kilos.

2.30 p.m.	Operation. ¼ gr. morphine and ether anæsthesia. 5 cm. loop of jejunum obstructed and vein ligated.
April 26.—	
12.15 p.m.	B.P. 115. Pulse 140. Dog quiet but able to walk. Given ¼ gr. morphine.
2.30 p.m.	B.P. 105. Pulse 70. Able to run about.
4.15 p.m.	B.P. 105. Pulse 80.
10.45 p.m.	B.P. 110. Pulse 180.
April 27.—	
Noon.	B.P. 90. Pulse 220. Mass palpable in upper left abdominal quadrant. Abdomen apparently tender on examination.
2.45 p.m.	Dead. Autopsy. No evidence of general peritonitis. Well localized cavity formed by coils of small intestine and omentum. Strangulated loop occupied centre of abscess cavity. Loop perforated and surrounded by grumous fluid. No free fluid in peritoneum. Distension of proximal loop.

Experiment 2 (April 25, 1932).—Bitch. Weight 10 kilos.

1.30 p.m.	Operation. 2½ cm. loop of jejunum obstructed and veins ligated.
April 26.—	
Noon.	B.P. 105. Pulse 160. Given ¼ gr. morphine. Dog able to walk but quiet.
2.0 p.m.	B.P. 105. Pulse 120.
4.0 p.m.	B.P. 105. Pulse 200.
11.0 p.m.	B.P. 100. Pulse 200.
April 27.—	
Noon.	B.P. 110. Pulse 180. Dog quite strong. Washed himself during morning. No mass palpable on examination.
3.0 p.m.	Laparotomy. Fair quantity of brown odourless fluid in peritoneum. Small omental mass found under left costal margin. Early and slight injection of mesentery and intestine. Jejunal loop found at centre of abscess cavity in omentum. Evident that dog had early peritonitis. Dog destroyed.

The first of these dogs lived forty-eight hours—at least twelve hours longer than any dog in the writer's series of strangulation of medium-sized loops. This animal had no widespread peritonitis, but died from the absorption of toxins from the abscess cavity, in the centre of which was found the perforated strangulated loop. The abscess cavity bore a striking resemblance

to that provided by an acute gangrenous appendicitis of the obstructive type in the human being. The second dog was in fairly good condition when it was destroyed over forty-eight hours after strangulation was produced. This dog had a very small loop strangulated, and the blood-pressure and pulse rate on the second day show how well the animal was able to cope with the small amounts of toxic substances produced by such a small loop. This dog had definite evidence of a spreading peritonitis and would have died probably within the next twenty-four hours.

All the experiments which have been considered up to date have dealt with internal strangulation—that is to say, where the loop is free within the peritoneal cavity. But so many strangulations in actual practice originate in a hernia, and the constriction at the neck of the hernial sac which produces strangulation also shuts off the contents of the sac from the general peritoneal cavity. It is well known that internal strangulation is more rapidly fatal than a corresponding external strangulation.[20] This is undoubtedly due to the fact that absorption from a hernial sac is much slower than from the peritoneal cavity. The capability of a dog to withstand the absorption of small amounts of the toxin is well shown in the last experiment. Forty-seven hours after strangulation this dog had a blood-pressure and pulse-rate very little changed from those taken twenty-four hours after strangulation. Yet this loop was intra-abdominal. It is quite certain that, had this loop been enclosed in a femoral hernial sac, the dog's condition would have been even better and there would have been no general peritonitis. Chenut[14] showed that life was prolonged in strangulation when the loop was placed extraperitoneally. It is along these lines that an explanation is to be found for the cases of strangulated femoral hernia of five or more days' duration which occasionally present themselves at general hospitals. The amount of toxin produced is not large and absorption is slowed to such an extent that the body is able to withstand the effects of its absorption. The strangulated loop forms a localized abscess the effects of which the body might conceivably survive were it not for the association of obstruction of the proximal portion of the small intestine. If left untreated, this in itself is capable of causing death. It is this obstruction which in late cases of small strangulated femoral herniæ is probably the main lethal factor.

STRANGULATION IN WHICH TOTAL ANÆMIA EXISTS.

This condition was investigated in 1924 by Foster and Hausler[10] and later by Wangensteen and Scott.[21] The condition occurs in practice very rarely, if at all. There is no blood lost into the loop and the acute collapse symptoms of the venous obstruction series are not shown. The loop is found at autopsy sometimes perforated, at other times intact but distended with gas. Well-marked evidence of a general peritonitis is always present at autopsy. The wall of the devitalized intestine is rapidly invaded by the intestinal flora. The loop usually becomes distended but from a different cause—the activity of gas-producing organisms. This distension has the effect of expressing fluid from the disintegrating tissues into the abdominal cavity. The fluid carries with it not only the products of the protein

metabolism taking place in the tissues but also the organisms responsible for the proteolysis. As a result the animal succumbs to a combination of a toxæmia, resulting from absorption of substances from the loop, and a generalized peritonitis.

THE NATURE OF THE TOXIN PRODUCED IN STRANGULATED LOOPS OF INTESTINE.

It is now universally accepted that the presence of bacteria in the lumen of the intestine is necessary for the production of the lethal substances which produce the toxæmia of acute intestinal strangulation. The bacterial origin of the toxin has been proved by the investigations of Dragstedt,[17] Murphy,[18] and their associates. The exact nature of the toxin is still doubtful. During recent years the interest of research workers has centred around the possibility that heat-labile toxins are the cause of the toxæmia of acute strangulation. This followed a paper published by Williams[22] in 1926, in which he suggested that the toxin produced by the *B. welchii* was, at least in part, the lethal agent in acute obstruction. McIver, White, and Lawson[13] tested this theory in relation to acute strangulation. They found from cultural studies of the bacterial flora of strangulated loops of bowel in cats that the number of *B. welchii* was always so increased that there was no doubt that this was the predominant organism. Further experiments showed that the organisms obtained were generally avirulent strains, and the administration of large doses of the *B. welchii* antitoxin failed to prolong the lives of animals with experimental acute strangulation. Other workers experimenting with a different type of acute obstruction were also unable to show that any benefit resulted from the use of the *B. welchii* antitoxin.[23-25] In consequence, it is no longer believed that the toxin of the *B. welchii* plays any important part in the toxæmia of acute intestinal obstruction. Williams[22] also made the very pertinent suggestion that the methods employed by many of the earlier workers,[26-28] which usually included heating of their preparations for varying periods, might result in the liberation of a toxic substance. He tested out his theory by heating for one hour the material obtained from patients and injected the Berkefeld filtrate into mice. His results suggested that a toxic substance was liberated from the intestinal contents by heating. My own experiments do not support this contention.

In these experiments the material was obtained from dogs in which an experimental strangulation had been produced. This choice was made because: (1) It had been previously shown that the fluid exuding from loops of intestine which had been strangulated for twenty hours or more contained toxic substances which caused death on absorption from the peritoneal cavity; and (2) A strangulated loop provides ideal cultural conditions for anaerobic organisms. The fluid used for injection was obtained in one of two ways: (1) From loops of intestine in which venous strangulation had been produced; or (2) By extracting with cold saline or water the tissues of intestinal loops to which both artery and veins had been tied. The loops of the venous strangulation series were all enclosed in rubber bags and left for a specified time in the abdominal cavity. In the arterial series the loops were either

incubated in rubber bags in the abdominal cavity or were incubated anaerobically *in vitro* at 37° C. Where filtration was carried out it was done in the cold, using a Berkefeld filter (gauge N). All injections were made intraperitoneally and small dogs were used for the purpose. The results are divided into two groups: (1) Those in which the fluid was obtained from loops in which a venous strangulation had been produced; and (2) Those in which an extract from loops with an arterial strangulation was used.

Results in Group I.—

	Hours Incubation	Filtered	Boiled	Result	
1	24	—	—	Dead	10 hrs.
2	24	—	Yes	Dead	4½ ,,
3	24	—	—	Dead	7 ,,
4	24	—	—	Dead	6 ,,
5	24	Yes	—	Well	—
6	24	Yes	—	Well	—
7	24	Yes	Yes	Well	—
8	24	Yes	Yes	Well	—

Results in Group II.—

	Incubated	Incubated	Filtered	Boiled	Result	
1	24	In vivo	—	—	Dead	6 hrs.
2	24	In vivo	—	—	Dead	10 ,,
3	36	In vivo	Yes	—	Well	—
4	36	In vivo	Yes	Yes	Well	—
5	24	In vitro	Yes	—	Well	—
6	24	In vitro	Yes	Yes	Well	—
7	24	In vitro	Yes	—	Well	—
8	24	In vitro	Yes	Yes	Well	—
9	48	In vitro	Yes	—	Well	—
10	48	In vitro	Yes	Yes	Well	—
11	48	In vitro	Yes	—	Well	—
12	48	In vitro	Yes	Yes	Well	—
13	24	In vitro	—	Yes	Well	—
14	24	In vitro	—	—	Dead	3 hrs.
15	24	In vitro	Yes	—	Dead	5 ,,

These results show quite definitely that Berkefeld filtration removes the toxic substances from the fluid. In one experiment only, No. 15 of Group II, was there a fatal result following the injection of a Berkefeld filtrate. In seven of the experiments the filtrate was boiled before the injection was made without any evidence of increased toxicity being demonstrated. All the animals very shortly after the injection was made showed well-marked evidence of histamine poisoning—namely, shivering, tremors of the hind limbs, salivation, vomiting, urination, and defæcation. These effects passed off within about half an hour and did not recur even in the animals which died.

These results are similar to those published by McIver and his associates.[13] They obtained their material from strangulated loops and injected various fractions intravenously into cats. They concluded that: (1) The crude loop contents were highly toxic; (2) The sediment obtained by centrifugation was highly toxic, but the supernatant fluid varied considerably in toxicity even though both the crude loop contents and the sediment from the same

animal were very toxic; (3) The filtrate resulting from Berkefeld filtration had no depressor effect on the blood-pressure. They also prepared a 'dialysate' obtained by removing the strangulated loop from the animal, suspending it in physiological salt solution and placing it in the incubator for two hours. The 'dialysate' was found to have a decided depressor effect and its toxicity was not destroyed by boiling for five minutes. These results appear to support the contention of the earlier workers who reported that the toxin was not destroyed by heat[6, 18, 29] and did not pass through a Berkefeld filter.[30] The toxin, though it is precipitated by five volumes of alcohol,[28] possesses no antigenic properties.[31] There is a striking similarity between the pharmacological actions of the toxic substance and those of the proteoses,[32, 33] and most workers[34] are agreed that the toxin is probably a proteose.

COMMENTARY.

From these experiments it is evident that the cause of death in venous strangulation depends directly on the length of bowel affected. With the onset of strangulation the loop of intestine becomes engorged with blood, rapidly at first but later decreasing as thrombosis spreads in the capillaries and small arterial twigs. The tissue spaces become distended with plasma and later with blood resulting from ruptured capillaries. When the loop of intestine is of sufficient length death takes place as a result of the rapid withdrawal of blood from the circulation. With loops of shorter length insufficient blood is lost to cause death, and thus other factors enter into the pathology. Quite soon after strangulation is produced the mucosa is invaded by the rapidly proliferating intestinal bacteria. The organisms spread to the deeper layers and find in the plasma filling the tissue spaces an ideal culture medium. The proteolytic anaerobes are the organisms which increase most rapidly in numbers. Meanwhile the loop of intestine is so distended with blood that large amounts of plasma pass through the peritoneal covering giving rise to the exudate which plays such an important part in the pathology of this condition. The exudate continues long after thrombosis is complete in the vessels of the loop.

The pressure within the lumen of the strangulated loop which was at first mainly due to a tonic contraction of the intestinal musculature is maintained, as the muscle dies, by the gas resulting from the action of the intestinal flora. It is probable that the distension of the loop which results from this gas production provides the mechanism by which the exudate from the loop is continued in the later stages. The exudate, which is at first indistinguishable from blood plasma, later becomes darker in colour and acquires a fœtid odour. An alteration in the toxicity of the fluid coincides with this change in appearance. The early exudate is non-toxic, but the exudate leaving the loop about twenty hours after the onset of strangulation is very toxic on absorption. At first it was thought that the exudate acquired its toxicity as the result of the permeation of the intestinal wall by the toxic substances present in the loop contents. Experimental evidence has been produced to show that it is doubtful if such permeation takes place, and, if it does, it is definitely insufficient in quantity to influence the result. The

toxic quality of the exudate in the later stages is the direct result of the action of the proteolytic organisms which have invaded the intestinal wall and tissue spaces in large numbers from the lumen. Chief amongst these organisms is the *B. welchii*, but the toxic qualities of exudate appear to be due to substances akin to the proteoses and not to any bacterial exotoxin. It is the absorption of the toxic exudate from the loop via the peritoneal cavity which is the cause of death in strangulation of intestinal loops of moderate length. When a small loop is strangulated the course of events proceeds a stage further. The amount of toxin escaping in the exudate is insufficient to cause death, and the disintegration of the intestinal wall continues until perforation takes place. Death may then occur as a result of the absorption of the toxic loop contents which have escaped into the peritoneal cavity, or from the widespread peritonitis which rapidly ensues. When very small loops of intestine are strangulated in extraperitoneal positions, e.g., femoral hernia, evidence has been brought forward which suggests that the dehydration resulting from the accompanying obstruction of the small intestine may be the lethal factor.

CLINICAL CONSIDERATIONS.

The subject matter of this paper has so far dealt solely with experimental strangulation. It is intended to indicate in this section the lines along which the results of the investigations already mentioned may be applied to the treatment of acute strangulation as it occurs in man. In all the experiments described in this paper strangulation has been produced by ligation of the mesenteric veins and, consequently, has been acute and complete. These conditions are not always—perhaps not even frequently—reproduced in clinical practice. In a typical case of strangulated hernia it is not usual for the venous drainage of the incarcerated loop of intestine to be suddenly and completely obstructed. At first there is a mild degree of venous obstruction which leads to some congestion and œdema of the intestine and mesentery which further obstructs the veins. In this way a vicious circle is set up which results in the venous obstruction becoming complete and the condition of strangulation developed. The case in which strangulation is present from the onset is usually characterized by such acute symptoms as to be unmistakable. It is obvious, therefore, that the various changes taking place in a strangulated loop will occur later in practice than is the case in experimental strangulation. This explains the apparent rapidity of the sequence of events in experimental strangulation.

An acute strangulation of the intestine in man which is comparable to the experimental long-loop strangulations is very uncommon. But there occur with reasonable frequency three allied conditions which, though generally not considered as such, are in effect strangulations. These are acute intussusception, mesenteric thrombosis, and certain cases of acute volvulus. In these conditions an interference with the blood-supply of a segment of intestine is an integral part of their pathology. In acute intussusception the venous drainage of the intussusception is obstructed before the condition has progressed very far, the intestine is acutely congested, and blood escapes into the lumen of the intussuscipiens, later producing the typical bloody

stools. In mesenteric thrombosis the venous obstruction takes some time to become complete, but again blood is lost into the loop. In acute volvulus the venous drainage may be completely obstructed at the time of the production of the volvulus, or the increasing distension of the loop may completely obstruct an already impaired venous drainage. But these conditions present two common features: (1) Long lengths of bowel may be affected; (2) A complete venous obstruction exists in the length of bowel affected. The blood loss, which is so marked a feature of the experimental long-loop strangulation, is equally evident in these clinical conditions. The shock which was previously attributed to twisting of the mesentery, pain, etc., has a more reasonable explanation. It is due to the withdrawal of blood from the circulation by the affected segment of intestine, and a blood transfusion is therefore an essential part of any treatment adopted.

The moderate-sized loops described in this paper have possibly more frequent clinical counterparts. They are still too long to occur frequently in strangulated external hernia, but do occur as internal strangulations. The cause of death in such cases has been shown to be the absorption of toxic products, formed in the wall of the intestine, from the peritoneal cavity. The danger of excessive manipulation of such loops lying within the abdomen is at once evident and the practice of exteriorizing such a loop immediately on discovery cannot be too strongly recommended.

The short loops occur frequently in clinical practice and fortunately present themselves as strangulated external herniæ and consequently receive prompt treatment. The fatal cases are usually those where there has been considerable delay in seeking treatment and the strangulated loop has become gangrenous and perforated, resulting usually in a widespread peritonitis.

There still remains a form of acute strangulation, which, though already mentioned, merits special consideration. This is the very small strangulated hernia, usually femoral, in which only a very small segment of bowel is affected or when the whole circumference of the gut is not involved, e.g., a Richter's hernia. In such a condition there is neither sufficient blood lost into the loop nor toxins absorbed from the loop to affect the patient's condition to any extent. Furthermore, the neck of the sac and the strangulated gut usually become sufficiently adherent to limit for the time being the infection which results from the perforation of the loop and which would otherwise spread back into the general abdominal cavity and lead to a generalized peritonitis. Such a patient may go on for several days until persistent vomiting and colicky abdominal pains force him to seek treatment. His general condition may then be very poor and surgical treatment a hazardous proceeding. But it should be borne in mind that his low general condition is the result of the obstruction of the intestine which naturally accompanies the strangulation. In the more massive strangulations the effect of superimposed obstruction is negligible, but in the type of case mentioned above it becomes of supreme importance The dehydration and chloride loss from repeated vomiting may assume such proportions as to become in themselves lethal factors. It is necessary in all such cases to combat the state of dehydration by the administration of adequate amounts of sodium chloride solution before surgical interference is considered.

The actual surgery of acute strangulation depends on the state of the intestine at operation. Any certain test of the viability or otherwise of strangulated intestine would be invaluable. Perhaps the most reliable of the various tests which have been used experimentally is the response of the gut to a strong faradic current. Intestine which fails to respond is definitely non-viable, but the converse does not always hold, and the test, in any case, is not likely to be generally useful. Any loop from which the peritoneal exudate has a fœtid odour should be regarded as non-viable. But experimental work has no reliable test of viability of strangulated intestine to offer. The time-honoured tests must be applied and one of two decisions reached. Gut must be regarded as definitely viable or non-viable. All doubtful cases should be regarded as non-viable, and under no circumstances should a doubtful loop of gut be returned to the abdomen. Such a loop should be brought out of the abdomen and a Paul's operation performed—in ill patients the loop may be excised the day following the operation. I believe it is safer to carry out such a procedure rather than attempt an immediate anastomosis, but this point is of secondary importance to the principle that all strangulated loops of doubtful viability should be resected.

CONCLUSIONS.

1. The duration of survival following venous strangulation of the intestine varies directly with the length of bowel affected.

a. When long loops are strangulated there is no evidence of any toxæmic process and death is due solely to the withholding of a large volume of blood from the circulation by the loop.

b. When moderate-sized loops of intestine are strangulated insufficient blood is withheld from the circulation to bring about a fatal issue, and death now results from the absorption, via the peritoneal cavity, of the fluid exuding from the loop, which becomes highly toxic about twenty hours after the onset of strangulation.

c. When short loops are strangulated there is neither sufficient blood withheld from the circulation nor toxins absorbed to cause death. Perforation of the loop always precedes death, which follows from the resulting widespread peritonitis aided by the absorption of the toxic loop contents. Only rarely will the latter be the sole agency to bring about a fatal result.

2. The toxic qualities of the peritoneal exudate from a strangulated loop result from the action of proteolytic organisms on the tissues of the intestinal wall. The exudate is not derived from the contents of the lumen of the loop.

3. There is no support for the view that bacterial exotoxins (e.g., *B. welchii*) are responsible for the toxæmia of acute strangulation. Evidence is brought forward which suggests that the toxin is of large molecular form and probably akin to the proteoses.

4. It is suggested that, when very small loops are strangulated in extra-peritoneal positions, e.g., femoral hernia, the cause of death is the dehydration resulting from the obstruction of the small intestine which accompanies the strangulation.

5. When the arteries as well as the veins are obstructed in strangulation death follows from a combination of toxæmia and peritonitis resulting from the action on and the penetration of the intestinal wall by bacteria from the lumen.

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NEUROSURGERY IN THE TREATMENT OF DISEASES OF THE PERIPHERAL BLOOD-VESSELS.

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Many contributions have been made during the last decade to the study and treatment of peripheral vascular disease. Since the pioneer work of A. W. Adson and his associates at the Mayo Clinic a new field in surgery has been opened. One of the earliest operations on the sympathetic nervous system was performed by Jaboulay in 1899, when he attempted to relieve painful conditions of the lower extremities by performing peri-arterial sympathectomy. Leriche brought this procedure to the notice of surgeons in 1913, when he advocated the operation for numerous peripheral vascular, trophic, and painful lesions. Following the work of Hunter, who postulated the sympathetic innervation of striated muscles in animals, Royle advocated ramisection for the relief of spasticity in cases of spastic paralysis. In attempting to duplicate the successful results which Royle reported in his series, Adson performed his first abdominal transperitoneal lumbar sympathetic ganglionectomy on May 20, 1924. He believed that some reduction of the spasticity was obtained, but attributed this to the increased blood-supply to the extremities following the complete interruption of vasomotor constrictor fibres. He based his operation on the belief that a more thorough denervation could be obtained in this way than by section of the rami communicantes alone. Experience has shown that this belief has been amply confirmed. However, as Adson has stated, "If the vasomotor fibres are divided by ramisectomy or by ganglionectomy and trunk resection it is immaterial which method is used so long as they are completely resected". The operation substantiates also the observations of Kramer and Todd, Potts, and Woollard that the innervation of the arteries and veins does not run centrifugally along the vessels, but that the vessels receive their innervation at various levels corresponding to the musculo-cutaneous segments.

It was following this operation that Adson made the historical observation that the temperature of the skin of the lower extremities remained permanently increased. This evidence of the change in temperature, which was due to an increased blood-flow following vasodilatation, led him to suggest that the operation might be applied to the relief of certain vasospastic diseases. Confirmation was first obtained by the pre-operative and post-operative calorimetric studies made by G. E. Brown on patients with spastic paralysis on whom Adson has performed sympathetic lumbar ganglionectomy and trunk resection. This report was encouraging in that it showed there was an average increase of 400 per cent in the elimination of heat following operation, and that the increase of heat production was permanent. Consequently

the operation was carried out for the first time by Adson for a case of Raynaud's disease of the lower extremities on March 19, 1925. The result was highly successful. Subsequent study showed that permanent vasodilatation was obtained and that the patient's symptoms were completely relieved.

Another contribution to the surgery of the sympathetic nervous system which was equally important was made by Adson in 1928, when he performed a bilateral cervico-thoracic ganglionectomy and trunk resection by the posterior intrathoracic approach. This approach was a modification of that first suggested by A. K. Henry in 1924 for the resection of the left cervico-thoracic ganglion in angina pectoris. The operation has entirely replaced the anterior or Jonnesco approach at the Mayo Clinic and elsewhere.

Following the successful results obtained in patients suffering from Raynaud's disease, the operation was extended to other diseases in which vasospastic phenomena were the outstanding features. It thus included thrombo-angiitis obliterans (Buerger's disease), in which the characteristic finding is occlusion of the main vessels associated with vasospasm of the collateral circulation. More recently it has been applied to certain types of scleroderma and chronic infective arthritis, in which a vasospastic element is present, and for subjective relief in anterior poliomyelitis.

In the wave of enthusiasm which has followed the publication of the successful results of treatment by sympathetic neurectomy, there have been instances in which the results have not been satisfactory. These have been mainly due to the selection of unsuitable cases. As Adson and Brown have stated, " With the advent of surgical procedures capable of producing arterial dilatation in the extremities, it becomes highly important to define clearly the types of vascular diseases that may be benefited by vasodilator measures. Considerable discrimination and caution should be employed in the selection of operable cases ". A study of a large series of cases in which operation has been performed during the last eight years has enabled them to formulate their opinions regarding the selectivity of cases, and these have again been more recently expressed by W. J. Mayo and Adson. They will be mentioned briefly below.

At the Mayo Clinic all cases are carefully studied and classified, not only on the condition of their vascular system and the response to vasodilating agents, as determined by cutaneous temperature studies, but on the present status and course of the disease.

The two diseases with which we are mainly concerned from a surgical standpoint are thrombo-angiitis obliterans and Raynaud's disease.

THROMBO-ANGIITIS OBLITERANS.

(*Buerger's Disease.*)

Thrombo-angiitis obliterans occurs almost exclusively in men between the age of 20 and 50 years. The youngest case reported at the Mayo Clinic was 17, the oldest 73 years. These cases are exceptional. Until lately it was thought that the disease occurred almost exclusively in Jews, but a recent analysis has shown that only 45 per cent of the cases occurred in Jews.

The majority of the patients are cigarette-smokers, and in a recent publication it has been shown by skin tests that they are unusually sensitive to tobacco. Furthermore, it has been shown by Barker that a certain degree of vasoconstriction occurs in normal persons during and after the smoking of several cigarettes. However, 5 per cent of cases of thrombo-angiitis obliterans have never smoked, while there are relatively very few cigarette-smokers who develop the disease. In a series of 240 cases the disease involved the lower extremities in 60 per cent, it affected the upper extremities alone in 2 per cent, and both upper and lower extremities in 38 per cent.

Superficial acute phlebitis is frequently seen in the course of the disease. Buerger and, more recently, Horton were able to produce inflammatory vascular changes in animals experimentally, by implantation of acutely inflamed veins. The investigations on the etiology of the disease are not yet conclusive. Adson is of the opinion that vasospasm may be the initial precipitating factor leading subsequently to thrombosis. In support of this, it has been observed that vasospasm, as evidenced by a phase in which the fingers or toes "go white and cold", is one of the features which is sometimes noted at the onset of the disease; while in another group of typical thrombo-angiitis obliterans of the lower extremities subsequent or coincident changes are seen in the vessels of the upper extremities which are highly suggestive of, if not indistinguishable from, Raynaud's disease.

In thrombo-angiitis obliterans the pathological picture is that of a chronic inflammation of the arteries and veins, mainly of the extremities, with a tendency to thrombosis. This depends on the duration and severity of the disease, and varies from slight thickening of the vessel wall to complete occlusion of the lumen by an organized thrombus with 'stiffening' of the wall. In the end-stages the arteries and veins and the accompanying nerves are usually bound up together by fibrous tissue consequent on proliferative changes. Microscopically there is infiltration of the adventitia, media, and intima, together with proliferative changes in all three layers, resulting in gross thickening of the vessel.

SYMPTOMS.

The symptoms of Buerger's disease are as follows: (1) Absence of arterial pulsation. (2) Claudication, trophic changes of the skin and nails, decreased skin temperature, and atrophy of muscles—all of which are the result of insufficient blood-supply. (3) Attacks of acute superficial phlebitis (in one-half of the cases). (4) Changes in colour of the extremities—pallor of the skin on elevation, and rubor on dependency of the extremity. The skin of the extremities is usually cold and red, which is the result of the contraction or spasm of the arterioles together with dilatation of the capillaries. (5) Rest pain, i. e., pain occurring in the absence of exercise. (6) Slow progression of the disease, frequently affecting first one extremity and then the other. (7) Acute ascending thrombosis of the artery occasionally. (8) Neuritic pains which occur as a result of ischæmia of the accompanying nerves.

In addition to the symptoms resulting from thrombosis of the vessels which have been outlined above, the vasospastic contraction of both the

diseased vessels and of the normal collateral vessels damages the remaining circulation. This observation is of prime importance in the treatment of the disease. Œdema of the lower extremities may complicate the clinical picture. X-rays of the peripheral arteries are usually negative, but in cases of doubt one can affirm the arterial occlusion by means of arteriography (*Fig.* 384). This procedure is one of academic interest rather than of clinical importance, as palpation of the vessels readily determines the presence or absence of pulsation.

FIG. 384.—Arteriogram of hand; showing absence of filling in many of the digital arteries and increased collateral circulation along the ulnar side of the hand.

Part of the impaired blood circulation, as has been noted above, is due to vasoconstriction of the arteries and arterioles. This must be eliminated and give place to vasodilatation in order to determine to what degree the interruption of vasoconstrictor impulses will result in a permanently improved circulation (*Fig.* 385). This can be done by the intravenous injection of non-specific foreign protein in the form of triple typhoid vaccine, as a result of which, during the fever reaction, all the arteries which are not occluded by thrombosis are opened to their maximum extent. Spinal anæsthesia produces the same effect, but is not usually employed for this purpose. The improvement in the circulation from the increased blood-flow can be measured by determining the difference in the skin temperature before and after injection of typhoid vaccine, the initial dose of which is usually 35 million. These values are formulated by Brown in the so-called vasomotor index. This is of great value in prognosticating the benefits that can be expected to result from sympathetic neurectomy. The index is obtained as follows: The skin temperature of the extremity and the body temperature of the patient are determined by the constant room temperature; following the injection of vaccine, an increase of the skin temperature and of the mouth temperature occurs. The temperature changes of the separate digits of all the extremities are measured by the thermocouple. Hourly readings are made until the maximal rise of fever has been obtained. The difference between the reading

of the skin and mouth temperature gives the indication for the existence of vasoconstriction. Thus the rise of the mouth temperature may be 2° C.; the rise of skin temperature in one digit may be 8° C.; the difference is 6, and this, divided by the rise in mouth temperature (2), gives a reading of 3—the vaso-motor index. The range of increased skin temperature of the extremity alone, e.g., from 25° C. to 35° C., indicates the amount of heat elimination resulting from vasodilatation, or, in other words, the increase in the peripheral circulation.

In cases of arteriosclerosis little change in the peripheral skin temperature can be demonstrated. This is also true of those cases of thrombo-angiitis

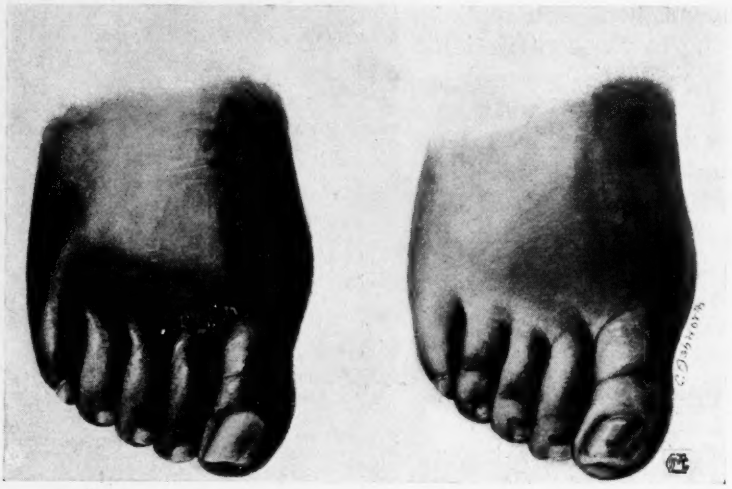

FIG. 385.—Colour changes in the feet in a case of thrombo-angiitis obliterans before and after sympathectomy.

obliterans in which most of the vessels are occluded as a result of organic changes; but in those cases in which the impaired circulation is in some measure caused by spasm of the collateral arteries the peripheral temperature will increase considerably. It may be mentioned that there are certain contra-indications for the administration of typhoid vaccine. These are: (1) Active tuberculosis; (2) Advanced arteriosclerosis, on account of the possible danger of producing myocardial thrombosis (P. S. Hench). For this reason vaccine is seldom given to patients who are more than 50 years of age.

TREATMENT.

Treatment of this condition depends on the stage and severity of the disease. Patients who show only the symptoms of claudication should be treated by a medical régime. This includes limitation of exercise, protection from trauma and cold, contrast baths, the so-called Buerger exercises (the foot elevated for one minute to 90°, held dependent for one minute, and then raised to the horizontal level for one minute). Dry heat is also of value. When the disease is progressive, rest in bed is essential together with the other forms of treatment. Vasodilatation produced by artificial fever may be used

to give temporary relief. Intravenous injection of triple typhoid vaccine, as used for the cutaneous temperature test, first of 25 million, then increasing the dose by 25 million twice a week, produces a moderate fever reaction which is accompanied by vasodilatation, and is the method that is most commonly used. Other ways of obtaining a temporary vasodilatation are intramuscular injections of sulphur, and acetylcholine. These are less effective than the injection of typhoid vaccine. Prompt but short-lasting vasodilatation can be obtained by giving alcohol by mouth. The results obtained by the injection of tissue extracts are still uncertain. Insulin-free pancreatic extracts are said to cause some vasodilatation, but experiments at the Mayo Clinic have shown that, if present at all, this reaction is only slight and evanescent. However, these extracts seem to have some beneficial influence on the disabling symptoms of claudication.

Patients in whom no pulsations of the peripheral vessels can be felt should be warned not to undergo any surgical operation, however trivial, on the extremities because superficial infections and small wounds—for example, in an operation for ingrowing toenail—heal very slowly on account of the inadequate blood-supply and may cause gangrene which finally necessitates amputation.

The results of medical treatment are far from ideal, though the number of amputations which have to be performed for this disease has been reduced from 25 per cent in untreated cases to 14 per cent in cases which have received adequate medical treatment, and to 5 per cent in those who have had sympathetic neurectomy performed in addition.

The beneficial effects of operation are due to the elimination of vasoconstrictor impulses to the peripheral vessels. This is accomplished by resection of the lumbar sympathetic ganglia with the intervening trunks when the lower extremities are involved. The second lumbar ganglion is usually the last ganglion to receive preganglionic fibres, the white rami communicantes, but in order to eliminate the possibility of rami reaching the sympathetic trunk at a lower level and conveying vasoconstrictor impulses, the third and fourth lumbar ganglia are always resected in addition. Access is obtained by a mid-line abdominal incision and incisions in the posterior peritoneum on each side. The details of the surgical technique need not be described more fully here. (*Figs.* 386, 387.)

In order to obtain a complete vasodilatation of the upper extremities, bilateral resection of the cervico-thoracic ganglia with the intervening trunk is performed. The posterior mid-line approach is used, with resection of a portion of the first rib and the transverse process of the first thoracic vertebra on each side. The inferior cervical and first thoracic ganglia with the upper portion of the thoracic trunk are removed. Usually the second thoracic ganglion can be removed through the same approach; all the ascending rami to the first thoracic and eighth cervical nerves should be divided (*Figs.* 388–390). The neurosurgeons at the Mayo Clinic believe this operation to be more thorough than the antero-superior approach, as the latter renders more difficult the removal of all the rami communicantes arising from the first and second thoracic ganglia.

As the sweat glands and sebaceous glands are innervated by fibres which are intermingled with the sympathetic vasoconstrictor nerves, the skin of

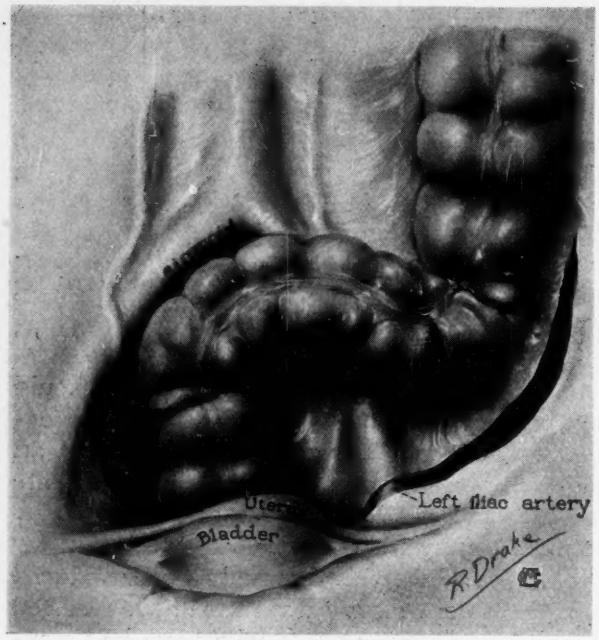

FIG. 386.—The incision in the lower left posterior portion of the peritoneum, permitting elevation and retraction of the sigmoid and descending colon medially.

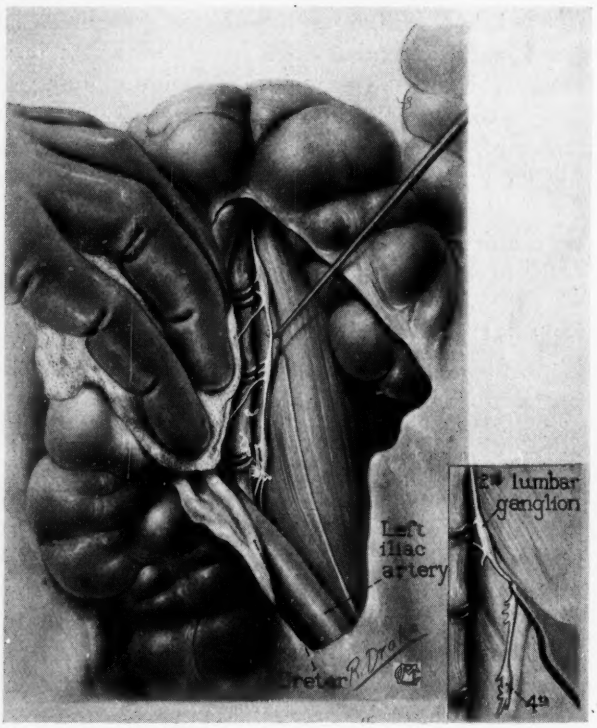

FIG. 387.—Exposure and resection of the left lumbar sympathetic trunk, with the second, third, and fourth lumbar ganglia.

the extremity after the operation becomes quite dry. Complete absence of sweating indicates that the operation has been complete; if present, the operation has been incomplete. In order to determine this point, the patient is placed in an electric 'baker', and strips of cobalt-blue paper are placed on the skin. In areas where there is sweating the colour of the paper changes to pink. Although post-ganglionic fibres to the hypogastric plexus are cut in the lumbar sympathectomy operation, sphincter disturbances never occur. Cervico-thoracic sympathectomy produces a Horner's syndrome, which, however, is hardly noticeable, and causes no disfigurement when a bilateral operation has been performed. It is interesting to observe that following a complete sympathetic neurectomy the extremities become warm, but no redness of the skin occurs. This indicates a dilatation of the arteries and arterioles, but not of the capillaries. This observation is confirmed by the fact that under the capillary microscope the capillaries are not dilated, but that the rate of the blood-flow is increased.

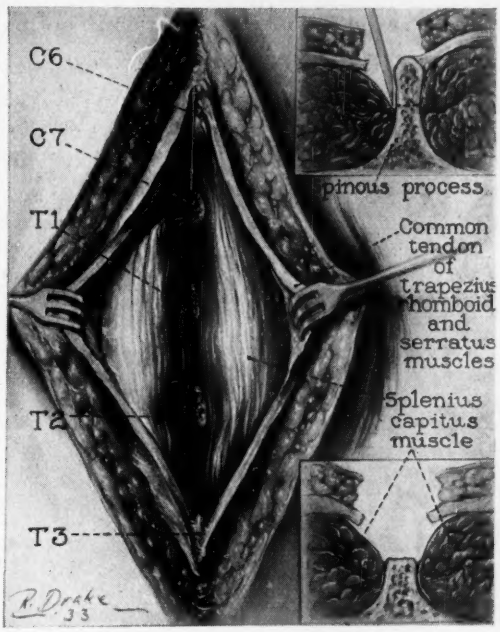

FIG. 388.—The dorsal mid-line incision with reflection of the common aponeurotic tendon of the trapezius, rhomboids, and serratus posterior muscles and resection of the spinous processes.

Selection of Cases.—The indications for the operation of sympathetic neurectomy are: (1) In those cases in which the vasomotor index is sufficiently high, or in which there is an adequate range of increased temperature in the extremities following the administration of typhoid vaccine. (2) In progressive cases in which unsatisfactory results are obtained by medical treatment. The contra-indications may be summarized briefly as follows: (1) The presence of acute fulminating ulceration. (2) Progressive gangrene. (3) Low vasomotor index, as obtained by the skin temperature tests. Brown states that unless the rise of temperature in the skin is at least twice as great as the rise in mouth temperature, operation is contra-indicated. In this connection Mayo and Adson also state, " It is obvious that vasodilatation cannot be produced in an arterio-sclerotic or occluded artery and that surgical intervention is useless unless there is positive evidence of vasospasm in the remaining non-occluded arteries ". (4) General contra-indications such as debility, cachexia, etc.

It is impossible to give more definite rules regarding the advisability of operation, as each offers an individual problem. It is well to hospitalize the patient a few weeks before operation in order to try to improve his circulation by a medical régime. Patients who present themselves with acute lesions, such as ulcers or gangrene, are not operated on until healing of the ulcer begins,

and in gangrenous digits until the line of demarcation between healthy and diseased tissue appears.

When sympathetic neurectomy is held to be contra-indicated amputation may have to be resorted to in certain cases. The most frequent indications for amputation are: (1) Progressive gangrene; (2) Uncontrollable pain in the presence of extensive occlusion of vessels which do not respond to vaso-dilating agents. It is often difficult to decide at what level to amputate. Occasionally an amputation of a toe or finger for a small area of superficial gangrene is successful, but usually a high amputation is indicated. If the popliteal artery is felt on examination to pulsate, amputation below the knee may be tried, but even then, in many cases, re-amputation above the knee

FIG. 389.—Exposure of first rib and transverse process of the first thoracic vertebra preliminary to resection.

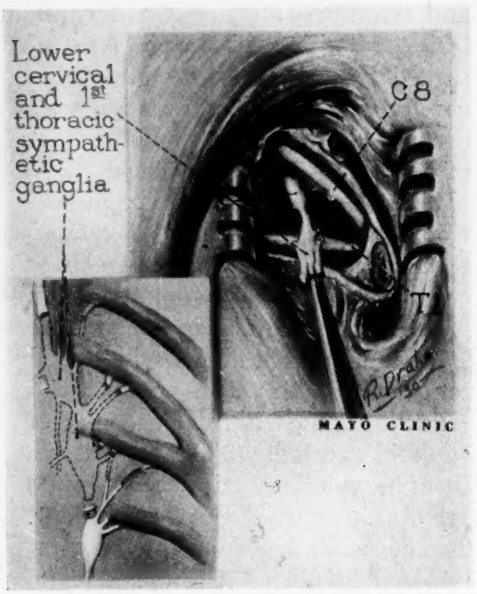

FIG. 390.—Resection of the lower cervical and first thoracic sympathetic ganglia with the trunk, and of rami extending from the second or third thoracic ganglia to the first thoracic and eighth cervical nerves.

will be necessary as the result of poor healing. Occasionally the amputation is complicated by gas-gangrene infection, which, however, is usually fairly benign.

Results.—A recent review of 100 consecutive cases of thrombo-angiitis obliterans showed that bilateral lumbar sympathetic ganglionectomy was done 89 times and cervico-thoracic sympathetic ganglionectomy 15 times. Four patients were operated on for the disease affecting both upper and lower extremities, which accounts for the 104 operations. There were 96 men and 4 women; the average age on admission was 35 years. Eighty-seven patients were markedly improved, with relief of pain and claudication assessed at an

average of 80 per cent, and improvement in the healing of ulcerating lesions of the skin. In the absence of advanced trophic lesions sympathectomy checked the progress of the disease in the opposite extremity in every case.

RAYNAUD'S DISEASE.

The main features of Raynaud's disease are so familiar that only a brief recapitulation is necessary. The disease should be differentiated from organic diseases of blood-vessels, for no organic changes in the vessels can be detected. There is, however, some vasomotor disturbance. Brown calls the condition a vasomotor neurosis of a spastic type. As a result of this disturbance, there are phases of symmetrical colour changes of the skin of the extremities, and sometimes of the nose and ears, associated with more or less severe pain. The arterial pulsations are present.

The disease is seen almost exclusively (about 80 per cent) in women, usually of the asthenic nervous type, and of a comparatively young age (average 31 years). The attacks are mostly precipitated by cold and exposure, resulting in contraction of the small arterioles, capillaries, and venules. When the skin in the acute phase is observed under the capillary microscope, only a small number of partially filled capillaries are seen. After a few moments, marked cyanosis of the extremities occurs. The stage of cyanosis is due to partial relaxation of the venules with a back-flow of blood in the capillary loops. During the last stage of the attack, increase of the temperature occurs spontaneously as a result of increased circulation following the opening of the capillaries, and the colour of the skin changes to red. All stages are seen between the almost normal response of the vessels to vasoconstrictor impulses induced by exposure to cold and the more severe attacks which follow only slight temperature changes, and in which there may be such complications as œdema of the extremities, trophic acral changes, dry ulcers, scleroderma, and occasionally gangrene.

The cause of the disease is unknown, but it is believed that the condition is of central origin in which there is an abnormal response on the part of the vasomotor centre, and that the local changes in the extremities are mediated through the vasomotor fibres. Krogh and Lewis, on the other hand, hold that the phenomena are due to a local cause associated with an abnormality digital arteries and arterioles, resulting in defective circulation.

TREATMENT.

The treatment of Raynaud's disease is dependent on the severity of the symptoms. In mild cases good results are obtained by eliminating the predisposing factors, e.g., by wearing warmer clothing and living in a warm, dry climate; but not all cases can be helped by these measures, and the severity of the symptoms together with the degree of disability may justify an operation. Cases have been reported in which temporary improvement was seen following the injection of typhoid vaccine.

The surgical treatment is essentially the same as that already described for thrombo-angiitis obliterans. As Raynaud's disease attacks the upper

extremities more frequently than the lower, it follows that cervico-thoracic sympathetic ganglionectomy and trunk resection is the usual operation. In a series of 54 cases, it was employed 39 times, while lumbar sympathetic ganglionectomy was employed 15 times. In the former group the average relief of pain and of colour changes in uncomplicated cases was 85 per cent, and in the latter group 100 per cent.

The incomplete results which are sometimes seen following operation on the upper extremities are apparently due to failure to resect all the vasomotor fibres. The more complete operation, as now advocated and practised, by including the second thoracic ganglion, the cervico-thoracic trunk, and all the rami going to the eighth cervical and to the first and second thoracic nerves, obviates the previous criticism and enhances the prognosis.

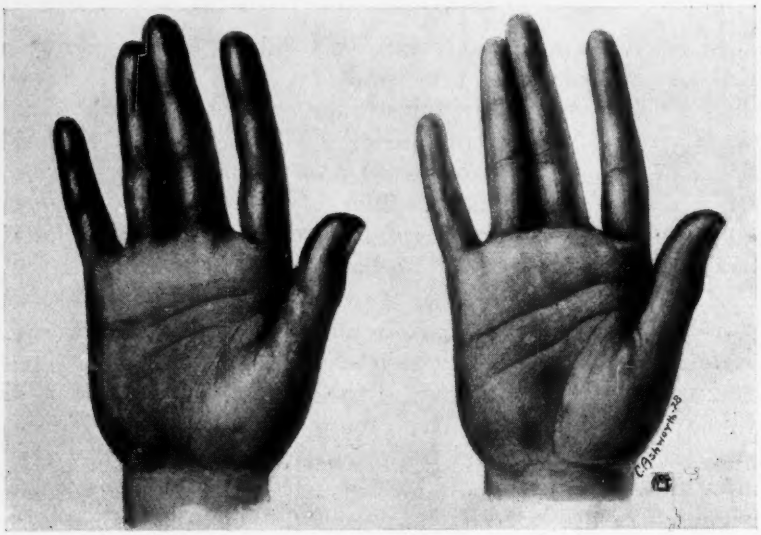

FIG. 391.—Colour changes in the hands in a case of Raynaud's disease before and after sympathectomy.

Therefore it can be said confidently that as a result of sympathetic neurectomy in Raynaud's disease the pain is relieved, abnormal colour reactions disappear, the skin of the extremities becomes pink in colour, dry, and warm, with a sustained increase in surface temperature. As Adson and Brown have stated, " The striking, maintained, and unequivocal therapeutic effects of lumbar and dorsal sympathetic ganglionectomy in Raynaud's disease seem to warrant the belief that surgical control in this disease is an accomplished fact." (*Fig.* 391.)

CASE REPORTS.

The following two cases are of interest in that they represent the extremes of the age-incidence group and were admitted consecutively at the clinic. The first was a woman, aged 52, and the second a girl, aged 11.

Both these patients had a bilateral cervico-thoracic sympathetic ganglionectomy performed, and the girl had in addition a bilateral lumbar sympathetic ganglionectomy.

Case 1.—Mrs. J. J., aged 52, was admitted to the clinic on Dec. 6, 1932. Her chief complaint was "numbness of the fingers and nervousness". She stated that she had suffered from many nervous breakdowns and gave way to frequent spells of crying. This nervous instability was made worse six years ago by the death of her husband, by her daughter's going blind, and by her mother's becoming insane. It was still further intensified by worrying over her present condition. Her present emotional stress amounted almost to an anxiety neurosis. Having become engrossed in the periodic attacks of numbness and colour changes that affected her fingers and toes, she related that she had spent much time in public libraries reading all the medical literature available, and that she had finally made her own diagnosis of Raynaud's disease. She then consulted forty-three doctors. They all stressed the nervous element in her condition and advised no active treatment. She remained unsatisfied, and, fortified by the comforting reports she had read of successful surgical treatment in other cases, she presented herself at the clinic with the firm intention of undergoing operation.

She had had numerous operations in the past: appendicectomy followed by peritonitis in 1910 and subsequently right salpingo-oöphorectomy, complicated by intestinal obstruction; drainage of a kidney abscess; tonsillectomy; and left femoral perivascular sympathectomy ten months ago. This last operation gave her no relief.

On Examination.—The patient was an obese (weight 188 lb.), well-developed elderly woman. Inquiry revealed that numbness and changes in colour in her fingers were first noticed sixteen years ago. These changes were brought on by cold and damp, and went through two phases, red and white. Several years later the toes were similarly involved. There was no pain at first. For the last three years the changes occurred in spasms which became progressively severe; in the fingers they were accompanied by pain, whereas in the toes there was numbness only. There was no constant stimulus, but the spasms were initiated by using the fingers as in sewing, particularly in damp weather and when exposed to the cold. The painful spasms in the fingers, according to the patient, formed a major disability, and she repeated her assertion many times that she would not rest until operation was performed. The numbness in her toes was unpleasant but not a disability. There were no trophic changes, ulceration, scleroderma, or arthritis.

The physical examination was otherwise negative, except for varicose veins in the right leg and slight loss of all types of sensation in the tips of the fingers and toes. Fundus examination showed a slight degree of sclerosis of the retinal arteries with structurally full discs; the eyes were otherwise negative. Urinalysis was negative except for slight albuminuria. Hæmatology: erythrocytes 4·54 million, leucocytes 6900, hæmoglobin 97 per cent, blood-sugar 105 mgrm., B.P. 128/90, pulse 80. Basal metabolic rate + 2. Flocculation tests were negative for syphilis. X-rays of the chest, spine, and extremities were negative. More detailed examination of the extremities showed that there was a two-phase colour reaction involving the fingers and toes. On elevation there was pallor associated with numbness, and on dependency there was rubor associated with tingling. The arterial pulsations were all normal, and there was no clinical evidence of organic obstruction or arteriosclerosis.

The cutaneous temperature tests and vasomotor studies were not completed in this case owing to the emotional distress that they produced. The consultant's note states, "Patient gets too emotionally upset to conclude any satisfactory studies regarding vasospasm of the hands. She says there has been no change since the tissue-extract was given; she says the hands feel as if they would change in colour if she went out, but this upsets her for the whole day and makes her so nervous, and gives her so much pain, that she cries even thinking about it. Therefore I would suggest discontinuing all studies meantime."

Operation was then advised because: (1) the condition was progressive but uncomplicated, (2) the pain during the spasms was intolerable, (3) the result should be good. The patient's age and emotional instability, in which the main factors were environmental, were not considered of themselves to be any contra-indication.

Operation.—On Dec. 15, 1932, Dr. Adson performed a bilateral cervico-thoracic sympathetic ganglionectomy and trunk resection under ether anæsthesia. The surgical card reads: "Approach through a mid-line dorsal incision. The common tendon of the trapezius, rhomboids, and the serratus posterior was elevated and subsequently closed after removal of the spinous processes of the first and second dorsal vertebræ. Entrance made through the first rib on each side. The ganglia were all about the usual size. The lower cervical ganglion on the left side presented a very beautiful stellate arrangement and communicated with the first thoracic by a broad trunk. The operation was comparatively easy, and there was no loss of blood. Prognosis should be good. Mortality less than 0·5 per cent".

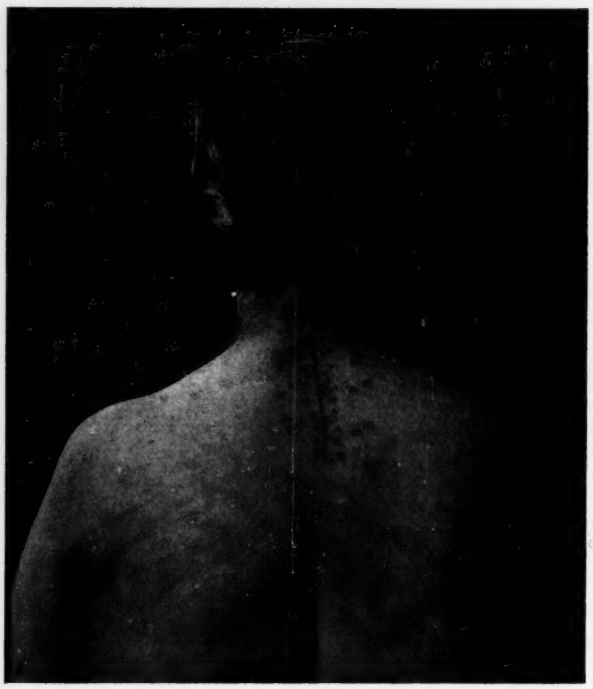

Fig. 392.—*Case* 1. The wound post-operatively, showing the extent of the incision.

Subsequent Progress.—Convalescence was satisfactory and the wound healed by primary intention (*Fig.* 392). The patient complained of indefinite pains in her joints and a little pain in the region of the right antecubital fossa. Twenty-five days after operation a sweating test showed that resection of sympathetic fibres had been complete. In this case there was no sweating from the shoulders to the finger-tips; elsewhere over the body sweating was profuse. There was a good gain in surface temperature as studied under normal room-temperature conditions. There were no colour changes in the hands when immersed in cold water. At the time of her dismissal on Jan. 11, 1933, the hands were dry and warm and it was clear that the circulation had been greatly improved.

On Jan. 19, her home doctor stated in a letter: "I was very glad to see her again and am much impressed by the good results of the operation". On March 18, the patient wrote as follows, "My back is doing nicely though it tires easily.

The circulation in my hands is practically very good. . . . I truly believe my whole nervous system has undergone a change. The tension has gone and I seem to be calm, cool and collected. . . . You know how happy I am."

Case 2.—L. M., a female, aged 11, was admitted to the clinic on Jan. 20, 1933. She complained of " all her fingers and toes turning dark blue every time they become the least bit cold ". Her family history was negative, although her mother was said to be " very nervous ". The patient had tonsillectomy performed three years ago; there were no other previous diseases or injuries.

On Examination.—She was a well-developed but rather thin little girl (weight 80 lb.), timid and shy on examination, but essentially of a rather unemotional and stolid type.

Her symptoms began about one year previously. At that time she had attacks of cyanosis and numbness of the fingers and toes, induced by exposure to cold. One month previous to admission she had noticed a small ulcer at the tip of her right index finger. The symptoms were practically absent during this last summer, but with the coming of autumn they re-appeared, and during this winter became much worse than ever before. She wore heavy gloves, but even then the fingers became very blue and cold; they also became swollen. There was no pain or tingling associated with the attacks, but a sensation of numbness. She complained of her fingers more than her toes. Her physical examination was essentially negative. There was some dental caries and a slight enlargement of the cervical glands. Urinalysis was negative. Hæmatology: erythrocytes 4·29 million, leucocytes 6900, sedimentation index 2·3, B.P. 120/60, pulse 72. Flocculation tests were negative. Eye examination was negative except for mild structural blurring of each disc. The X-ray examination of the chest, hands, and feet was negative. The central nervous system was negative.

The fingers and toes were blue and cold. The index and middle fingers of the right hand were swollen. The ulcer on the tip of the index finger was close under the nail; it measured about 7 mm. in diameter and was surrounded by concentric layers of thin desquamated skin. There was beginning desquamation at the tip of the middle finger but no actual ulceration. The cold test was negative for hypertension or for a pre-hypertension state.

On Jan. 26, 1933, the vasomotor test resulted as follows (the readings in Centigrade):—

Digit	Initial Temperature	Maximum Temperature	Range of Temperature	Rise in Mouth Temperature	Index
Right 2 F. ..	25·5°	32·8°	7·3°	1·1°	5·6
Left 2 F. ..	27·0°	34·7°	7·7°	—	6·6
Right 1 T. ..	24·1°	35·6°	11·5°	—	9·4
Left 1 T. ..	24·0°	36·5°	12·5°	—	10·3

Conclusion: " Good vasodilation; adequate for operation."

Thus a diagnosis was made of Raynaud's disease involving both upper and lower extremities, with secondary thrombosis and occlusion of the digital arteries, especially that of the right index finger.

First Operation.—On Jan. 31, 1933, Dr. Adson performed a bilateral cervicothoracic sympathetic ganglionectomy and trunk resection under ether anæsthesia. Approach was made by the usual method with resection of a portion of the first rib on each side. The ganglia were normal in size and distribution.

Course.—The patient's convalescence following this operation was entirely uneventful. After the vasodilating effects of the anæsthetic had worn off and could be discounted the hands remained persistently warm, dry, and pink. The small trophic lesions on the tips of the middle and index fingers of the right hand began to heal immediately. There was a definite Horner's syndrome on each side. On March 8, thirty-seven days after operation, a sweating test showed that a complete operation had been performed, with interruption of all the vasomotor fibres to all the sweat glands of the upper extremities (*Fig.* 393).

SECOND OPERATION.—On Feb. 20, twenty-one days after the previous operation, the patient had convalesced sufficiently well to permit of the second operation for the relief of the disease affecting the lower extremities. Consequently a bilateral lumbar sympathetic ganglionectomy and trunk resection was carried out under ether anæsthesia by Dr. Adson. The usual transperitoneal approach was used, with incisions lateral to the cæcum and to the pelvic colon in turn. The abdominal and pelvic viscera were normal. The ganglia were easily exposed, and the second, third, and fourth with the intervening trunk were removed on each side. They were of the usual size, shape, and distribution. The wound was closed in the usual manner.

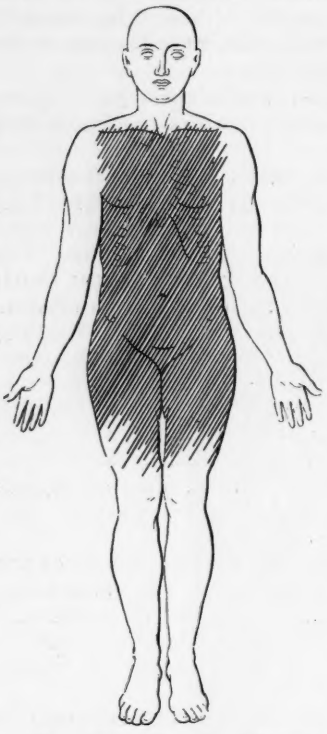

FIG. 393.—*Case* 2. Diagram illustrating the result of operation following the sweating test: the absence of sweating is indicated by the non-shaded areas.

SUBSEQUENT PROGRESS.—Following the second operation the patient's convalescence was again without incident. The feet and toes became warm and dry and "very comfortable". There were no symptoms or changes in the normal function of the bladder and bowel. On March 7, fifteen days later, the skin temperature of the hands and feet under normal room conditions was determined by hourly readings for six hours. The results were as follows:—

Right foot	..	32·6° C. (aver.)
Left foot	..	32·4° C. („)
Right hand (dorsum)	..	31·8° C. („)
Left hand (dorsum)	..	32·8° C. („)

This test showed that an average high level of surface temperature was maintained, and indicated that a definite and persistent increase in the peripheral circulation had been accomplished.

On March 11, nineteen days after the second operation, the patient was allowed to return home. The post-operative convalescence record, in summing up stated, "There was a striking improvement in the condition of the hands and the feet. They were warm and dry, and all her symptoms were entirely relieved."

This communication is a brief outline of the views held and the treatment employed at the Mayo Clinic in regard to certain vascular diseases which I have had a special opportunity of studying during the tenure of a Rockefeller Travelling Fellowship. While it is realized that many aspects of these diseases are familiar to those who are engaged in work in this field elsewhere, it seemed that the above descriptions might be of interest to others who are not engaged in a special study of the subject.

My thanks are due in particular to Dr. A. W. Adson, for whom I had the privilege of acting as First Assistant, for his permission to make full use of his personal statements and publications.

THE SELENIDE TREATMENT OF CANCER.

By A. T. TODD,

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I commenced active research on the treatment of cancer about 1926; at that time treatment by what was called 'colloidal lead' was much to the fore. As I did not wish simply to repeat the work of others, I decided to try to combine the possible action of lead with that of selenium. Selenium was first used on a scientific basis by von Wassermann,[1] and on one occasion the results were promising. It appeared possible that the combination of two agents might be more effective than either singly. Therefore I had lead selenide made in colloidal form, and after careful toxicity experiments on animals, employed it in cases of guaranteed inoperable cancer.

This selenide, called 'D4S', has been on the market for five years. My results from its use were good, all things considered. Of the cases treated, 10 per cent can be claimed as four-year cures. About 50 per cent of the cases showed marked prolongation of life, with comfort as a rule. Its analgesic effect is often marked, giving relief when morphine and other analgesics fail. But this system of treatment was slow and required much care on the part of the practitioner and much co-operation from the patient; in addition, as in all chronic diseases, it requires that the practitioner shall convey his real, or assumed, belief in the efficacy of the treatment. Care in dosage is essential: too small dosage gives no result; too large dosage hastens the growth of the neoplasm. I still maintain that this system[4] should be employed as a routine for a year after presumed complete operation; in view of my results it appears highly probable that a reduction in the number of recurrences would follow. But from now onwards the colloid R.A.S. should be substituted for the old D4S.

Certain of my cases failed to benefit from this selenide, completely or in part. I determined, therefore, to try if its action could be augmented by concurrent radiation from X rays and radium. The cases were treated cautiously and never received more than half the total dosage which would have been given to a case treated exclusively with radiation. The result was disappointing at first sight, and certainly surprising; on applying radiation in the usual dosage to cases impregnated with lead selenide there always followed a striking and rapid intensification of the growth of the neoplasm; cases which had been stationary for months would die within a few weeks of acute cancerous invasion. This happened in twelve consecutive cases. Concurrent radiation was stopped in man and repeated on mice with implanted Twort carcinoma, with the same result—radiation on a mouse impregnated with lead selenide caused intensification of the rate of growth of the implant.[2]

The significance of this finding was not grasped at first, for a good deal of experimental work was necessary. It was found that massive dosage of D4S—that is, the largest doses tolerable by man or animal—gave the same response, a marked and prompt acceleration of neoplastic growth. Possible explanations were: (1) That radiation had in some way intensified the action of the colloid and so converted a small into a large dose: from the work of others and ourselves[2] this result must be due to the selenium, for radiation after lead colloids free from selenium does not give this result. Or (2) That the presence of the selenide had converted a relatively small into a relatively large dose of radiation; for my experience is that, with the exception of a few types of specially sensitive growths, intensive radiation also has a stimulating action on neoplastic growth.

The second of these hypotheses appeared to be the more attractive, and steps were taken to make another selenium colloid which would be more amenable to combined colloid-radiation therapy. We found that by reducing selenium dioxide in the presence of my sulphur colloid, selenium was taken up and a double colloid of sulphur and selenium resulted. We call this new colloid 'SSe', and it will be liberated for general use on publication of this article.

To appear to digress for a while. It may be asked: Why so much talk about colloids? To my mind the disease cancer is closely related to the granulomata, the connecting link being lymphadenoma. Partial proof has been afforded recently that the latter disease is due to a virus. I had become convinced long before this that cancer was an infective disease and probably due to growth stimulation from the presence of a virus. I admit that final proof is not yet attained, but if the evidence is weighed without bias, there is little case for any other conception. Space does not permit me to go into this question more fully. I considered, then, that cancer was an infective disease and that a defence mechanism of mesoblastic tissues was present, but that this defence always failed. This tissue I called 'junction tissue', and I gave some proof that chronicity and radio-sensitivity of a cancer were, as a rule, proportional to the amount of this junction tissue.[3] It consists of fibroblasts, lymphocytes, plasma cells, eosinophils, basophils, and macrophage cells. From our knowledge of defence mechanisms in other diseases we should regard the macrophages as the key cells, as they appear to govern the function of the others. These macrophages can only be influenced by colloids; they engulf any electro-negative colloidal particle. If the particle is incapable of being broken down by the enzymes of the macrophage, it is simply stored or passed away into the lymph channels. But if the particle can be chemically altered by the cell enzymes, there are several possibilities: some innocuous compound may result; a substance poisonous to the cell which has produced it may be formed; a compound which stimulates the metabolism of the cell may result. Thus a colloid is essential, and intravenous administration will be necessary for certain access to the macrophage system.

In brief, then, cancer is regarded as an infective disease with a defence mechanism; a system of treatment which should increase this defence was attempted; if stimulation of the defence then became adequate, the growth

of the neoplasm should be inhibited. That is, the action of the treatment in cancer, as in the other chronic diseases, should be in assisting the process of natural cure, for direct action, to try to poison the disease tissue itself, has completely failed.

This hypothesis demands proof, and we can give a certain amount. Radiation alone increases the amount of junction tissue, macrophage included, if correct dosage is employed. Lead selenide alone, and lead selenide after radiation, give the same result, and with increase of junction tissue there is atrophy of the neoplastic tissue. But radiation of the same dosage after treatment with lead selenide caused a poverty of junction tissue, usually disappearance of macrophages, and an increased rate of growth of the implant.[3]

The newer method of treatment consists of radiation plus intravenous injection of selenium colloids. Have we any sort of proof that radiation can act upon and alter the selenium particle? There is a good deal of proof existent. The alteration in the conductivity of selenium from radiation of light rays is the basis of the action of the selenium cell, which is widely used in sound films, burglar-traps, some traffic signals, and television. It was known that X rays and gamma rays also produced a change; this change is called 'ionization' by the physicists, and for this reason I have called the new method the 'ionization method'. I do not specifically claim that such ionization is the cause of the results obtained, but that it may be the cause. I do claim that some change follows the application of deep X and gamma rays to a tissue impregnated with this new selenium colloid, and we have collected a certain amount of proof.

1. *Physical.*—Radiation by sunlight flocculates the colloid and the selenium migrates towards the radiation. On pure selenium, the selenium bridge, we find that X rays produce a rapid increase of conductivity; heat rays have the opposite effect, but less rapid. Radium rays slowly and steadily increase conductivity up to twenty-four hours, the time-limit of our experiments. We have also tested the effect of the shorter Hertzian waves, those with a wave-length of about 4 metres. Here I should like to thank Marconi Company Ltd. for their generosity in lending us the necessary apparatus. On tuning the external circuit we find a sharp increase of conductivity for a short period, then a steady diminution—the latter being due to the heat effect, but tuning and detuning still show smartly. A selenium colloid was prepared as free from electrolytes as possible; this has also been tested against the same types of radiation; X rays, radium rays, and Hertzian rays all show a diminution of conductivity. This contradiction is only apparent, for the current is carried by the electrolytes and not the colloidal particles; the latter are ionized, however, and then adsorb electrolyte and thus diminish conductivity. The selenium colloid which we use does not show this effect, for there is so much available electrolyte that any ionization effect is masked *in vitro*. A sulphur and a tellurium colloid do not give these results.

2. *Biological.*—The evidence on mice has been noted; radium radiation after impregnation with lead selenide sol regularly produced acceleration of neoplastic growth and atrophy of junction tissue. A long series of experiments on radio-sensitive protozoa has been carried out. To cultures of the

protozoa various colloids were added and the result of radium radiation observed. In the presence of suitable amounts of selenium sols, radiation steadily increased the death-rate as compared with non-radiated cultures. Sulphur sols had the opposite action. A tellurium sol had no effect.

3. *Clinical.*—The clinical proof is, in the main, the success or otherwise of the system of treatment, and I think the results will speak for that. Patients are only accepted into my clinic after they have been given up by surgeon, radiologist, and radium officer. Most of them have already been treated by their methods before I take them, and treatment has, of course, failed. All the cases are advanced, and fully a fifth can be regarded as moribund. It is quite often found that a patient has died before a bed has become available, although cancer cases are given priority. I think it will be conceded that a high rate of two- to four-year cures is not to be expected in such material. Until quite recently no selection of cases has been made; if there was room for the patient, then the patient was taken.

That an action on the patient does follow the application of X-radiation will quickly become apparent to those who follow the system. After an intravenous injection of SSe there may be some trivial and evanescent effects such as cough or a short rigor; then, three to twelve hours later, true focal reaction sets in. This consists of intensification of the symptoms produced by the neoplasm, and, when superficial, it is frequently seen that congestion and some œdema have appeared around the growth. This focal reaction passes off in a longer or shorter time, and then there is usually freedom from pain and general euphoria. Two days later, this time to allow effective storage by the macrophage system, and to be well over the reaction produced by the colloid, the dose of deep X rays is applied. If the dose is adequate, focal reaction appears again, but with a much shorter latent period. If a non-selenium colloid is administered, there is no focal reaction and the same dose of X rays produces no result. This has been done on many occasions, in order to exclude any factor of suggestion. The same dose of X rays at a 12- to 16-day interval after colloid injection also produces no result. This finding was not expected; it is simply what has been found. As the only change in selenium on radiation is ionization, I call the method the 'ionization method'. Mr. C. Joll, in his recent Long Fox Lecture, criticized my system on account of this name; he stated that certain physicists had assured him that the amount of ionization reproduced from the dosages I use would be inadequate; I think they meant 'inadequate to kill the cancer', and there I agree, for no attempt is made to kill the cancer directly. I do not think they can deny that this trivial ionization might stimulate the macrophage system. Proof of ionization in the living subject is quite impossible.

Later it appeared to be desirable to determine whether a radio-active selenium colloid might be effective; if ionization does occur, then the taking up of such a colloid into the macrophage system in the junction tissue should allow feeble, but continuous, ionization at the site itself. Radium residues, consisting of radium G and traces of the higher breakdown products of disintegration, were converted into colloidal selenides in a manner similar to that employed for D4S. We call this newer colloid 'R.A.S.' It is very similar in its appearance and properties to D4S and is quite stable in the

absence of oxygen. It is feebly radio-active, but I have not the facilities to measure its exact intensity; it does slowly blacken a photographic plate protected by light-proof paper. Its toxicity to man and animals is very similar to that of D4S, but its local action in causing obliterative endophlebitis is much less marked. It was seldom possible to get more than an average of six intravenous injections in mice with D4S, but with R.A.S. weekly injections can be made almost indefinitely. The results on the slow-growing strain of Twort carcinoma we propagate are much better than those given by D4S; with the latter we averaged about 10 per cent of regressions, but with R.A.S. we now get a steady 25 per cent.

The parenteral administration of radium salts is highly dangerous; the results, mostly from the United States, show that some fatal disease is almost an invariable sequel—osteomalacia, anæmia, leukæmia, or osteogenetic sarcoma. R.A.S. has a very much more feeble radio-activity than any pure radium salt, and though it has been employed in man for two years, no ill effects have been observed. But as two years is a shorter time than is the latent period of the diseases noted, a number of animal experiments have been carried out. Mice and rabbits have been injected with as large doses as they would tolerate for a time, then observed for six months; this period corresponds to about twenty years man/mouse and seven years for man/rabbit. The animals remained well as far as could be seen. They were killed and examined histologically after death. No abnormalities were found.

The last new remedy in the system is Paré's ointment. Ambroise Paré treated malignant ulcers by filling the cavity with a sheet of lead cut to shape and rubbed over with mercury. He claimed that it was a useful treatment, and he was a very accurate observer. I considered that a much more powerful action would be likely from the use of finely powdered lead amalgam embodied in an ointment. I think that it is really a useful application for malignant ulcers, or threatened ulcers, except those so near the mouth that poisoning would be likely: it has an antiseptic action, probably from breaking off of mercury salts. Patients are to be warned of its highly poisonous quality if taken by the mouth, and are advised to wash thoroughly after applying it. Nurses are advised to wear gloves. No case of poisoning has occurred in the clinic. I have never employed it alone, so that its potency is uncertain. It is manufactured by British Drug Houses Ltd., just as are the two newer colloids, SSe and R.A.S.

I have been criticized for not liberating methods of manufacture wholly and fully. There are several reasons why I have not. Firstly the medical journals would not welcome a very long purely technical account of the methods, and a full description would necessitate a long article. Then these selenium colloids require great technical exactitude in manufacture if a non-toxic colloid is to result; trivial impurities, in distilled water, for instance, will produce a colloid of high toxicity. The firm selected for its high status was requested to send a chemist to the Bristol laboratories to be taught the method of manufacture; thus colloids exactly similar to those we use are produced. I feel certain that if this precaution had not been taken, firms would have produced colloidal preparations of differing properties from those

we used. They would have done so quite unknowingly, but then these findings would have been discredited.*

THE TECHNIQUE OF THE NEWER METHOD.

The patient is warned that treatment will be prolonged, extending over years, if the result is favourable; a weekly attendance will be necessary. If he cannot engage to do this, then he is not accepted for treatment. Of late the moron type has not been accepted, for co-operation is impossible. Carcinoma of the alimentary tract with hepatic metastases is only accepted if the primary is capable of removal, for while primary colon requires high dosage, hepatic metastasis requires low dosage. Other than this, no selection is made, and until recently no selection whatever was made. Every case has to be guaranteed untreatable and to be free of diagnostic doubt.

When surgical removal of a reasonably large part of the mass is regarded as a fairly safe procedure, the patient is referred back to the surgeon for what we call the 'toilet operation'; this is especially desirable in septic fungations, for sepsis causes false reaction and one is impeded in assessing true reactivity. Even in non-septic cases removal of as much as possible is desirable on first principles, as this leaves less for us to deal with. Such a toilet certainly improves results, but, breast cases excepted, it is not often possible. In a toilet operation difficult glands are not removed. In cases with rapidly-growing carcinoma, such as encephaloid of the breast, or sarcoma, one or two weeks of ionization are given before the toilet, with the object of getting some inhibition. Occasionally this preliminary has been so successful that toilet, or biopsy operation, has had to be put off altogether, as in the following case:—

Dav.—Sent to me by Professor Rendle Short. There was a large, rapidly growing lump springing from the pubis and extending upwards and backwards, involving the bladder, judging from the dysuria and frequency. The patient had lost much weight and become very weak. X rays showed a shadow less dense than bone but apparently containing some strands of ossification or calcification. The mass was about the size of a grape fruit. We decided to postpone biopsy until growth was stopped. On treatment rapid diminution in size took place and any interference was considered unjustified. The man has been discharged for two years and now is at work as a coal-hewer.

Next tests of blood and reactivity, purely for research purposes, are made, and then the patient is started on the medicinal and other treatment. As I have on several occasions given the rationale of the drug treatment,[4] I will not repeat it; each patient takes $\frac{1}{10}$ gr. of dry thyroid extract once daily; three to six drops of radiostoleum daily; three doses of mist. calci thiosulphate (sol. calc. thiosulphate, 50 per cent, min. 40; glucose gr. 20; inf. caryoph. (1–7) $\frac{1}{2}$ fl. oz.; water to 1 fl. oz.; this replaces the older mist. calci chlorid. alb.) plus 5 gr. of sodium iodide after meals. If pain is experienced, we give aspirin, tab. amidopyrin co. (B.D.H.), allonal, or the other analgesics, morphine group excepted. As a last resort we give heroin, but

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* No royalties whatsoever are paid directly or indirectly.

few cases respond unless its administration can soon be stopped. Many of the patients have been on large doses of morphine before they come to us; as a rule we are soon able to discontinue it. Pain usually lessens at an early stage of treatment; a case under treatment at the present time illustrates this:—

Cat.—Breast removed in Chicago; secondary deposits appeared in the lumbar spine and she was treated with some form of colloidal lead, probably the phosphate. Being aware of the diagnosis, she determined to come to England to see relatives before it was too late. She was treated at Cambridge and London by deep X-ray therapy, but went downhill. She was sent to my clinic, the surgeon reporting her condition as deplorable, as it really was. She had intense pain on movement and at rest; she vomited all she ate. Large doses of morphine gave little relief. Skiagrams showed large deposits in lumbar spine and ilium. She was treated by the method I am about to describe, and within a week was able to do without sedatives. Her pains disappeared and she was able to get up for a time. Later, mental blunting, transient diplopia, and choked disc indicated a cerebral metastasis; this is now being treated, the result at present being doubtful.

The tests noted below being completed, the radiologist is asked to give a time for treatment, and approximately forty-eight hours before this date an intravenous injection of SSe is given. The size of the initial dose varies with the size of the patient and the type of neoplasm. Sarcoma, rapidly-growing carcinoma, ovarian carcinoma, and hepatic growths are likely to be sensitive: an initial dose of 2·0 c.c. will probably be safe. Other types will start with 4·0 c.c. Reaction is awaited and its magnitude is noted. We try to avoid more than appreciable reaction; if much followed the first dose, the second dose will be reduced. If no reaction follows, then the dose is increased by 1·0 c.c. for sensitive, and 2·0 c.c. for non-sensitive, cases. This is repeated each week till reaction is obtained; but once the reactive dose is found, that dose is continued till reaction tends to wane, when again an increase is made. Pyrexial conditions, such as colds, increase reaction; if present, we make it a rule to halve the size of the injection.

After forty-eight hours the patient is radiated, and the first treatment is over the main mass, or, if pain is present, over the painful part. The dose given is $1\frac{1}{2}$ Holtznecht units, distance 30 in., 180 K.V., screen 0·3 mm. zinc. This dose is repeated weekly until 12 H. units have been given; but in a case not responding, we sometimes continue up to 20 H. units before stopping. After each application X-ray reaction is looked for; if it is marked, the dose of X rays is reduced the next time; if not present, and the colloid reaction was adequate, the X-ray dose is increased. If X-ray reaction is slight and colloid reaction trivial, then the colloid dose is increased first and X-ray dose increased later, if reaction is still absent.

When the first ionization course is over the patient begins alternation of colloids. He attends weekly and is questioned about symptoms, etc., and is given new supplies of medicines. For the first three weeks he is given R.A.S., the first dose being about two-thirds the amount of his last dose of SSe. If marked reaction follows, the second is lessened. Always just appreciable reaction is aimed at. After this three weeks, he has alternately one week SSe, the next R.A.S. For pyrexial interludes the dose of SSe is halved, but if it is a week for R.A.S. we substitute SSe instead. This alternation is to permit a slow, progressive ionization from the radiation of the R.A.S.

If progress is in doubt, or signs of extending growth appear, he is again started on ionization from X rays, but we do not like to do this within three months from the termination of the last course. If progress appears to be satisfactory, alternation is continued for at least six months, when a holiday from injections is given for about eight to ten weeks. After this, if progress is satisfactory, alternation continues; if unsatisfactory, ionization followed by alternation. When progress has continued satisfactory for about nine months, no colloids are given, the patient simply attends for observation and medicines. After six months of observation he is discharged, but told to attend at once if any suspicious symptom appears. So far no discharged case has ever returned with active disease of the type originally treated; one patient with mammary carcinoma did return after nine months of discharge with what appeared to be encephalitis. She died, and autopsy revealed primary carcinoma of the pituitary; no mammary growth was found.

Reaction.—It is important that a correct idea of what is meant by reaction should be obtained by practitioner and patient. Reaction means a definite, but moderate, aggravation of the symptoms produced spontaneously by the neoplasm. If may be severe if the initial dose is too great; it will tend to be severe if there is a coryza or similar pyrexic malady, but exclusive of these there should not be severe reaction. Severe reaction may be fatal; if not, it will probably make the patient avoid further treatment; lastly, I have never seen anything but harm follow a series of severe reactions.

PROGNOSIS.

If the neoplasm is visible or palpable, increase or decrease may be obvious. Increase in size, at first, may not mean that the neoplasm is growing, it may be due simply to increase of junction tissue. Gain in weight, when weight has been lost, is favourable. Loss of pain is good, especially if it continues, but most cases get some relief of pain even though ultimately not responsive. The general condition of the patient as regards appetite and gain in strength is important; these may be unsatisfactory in the specially sensitive neoplasms when doing well. Sometimes, when breakdown is rapid, the patient appears to be going downhill rapidly; but if the masses are found to be diminishing, treatment should continue, though ionization should either be given longer intervals or be stopped for a time. At times the patient is nearly killed from the absorption of the products of breakdown. The following case is an example:—

Par.—Sent by Mr. Hey Groves. A large mass about the size of a melon but flatter, was situated on the ilium, extending up into the lumbar muscles and down into the thigh, growth rapid. Biopsy diagnosed a highly malignant endothelioma (Professor M. Stewart) or polymorph sarcoma (Dr. A. L. Taylor). Reaction to small doses of SSe was marked, and consistently smaller doses were given; reaction to X rays was also great and the patient was reduced to 1 H. unit. The mass rapidly began to diminish, but general toxæmia became so marked that ionization was stopped at 6 H. units. He was then very ill, had no strength, and was unable to retain food. For two months small doses of D4S were given weekly, as reaction from this is less and slower than from the newer colloids. He gradually picked up and was put on alternation, with gradual increase of dosage as his tolerance

permitted. The mass disappeared and his health became normal except for a gradual increase of adiposity—this happens not infrequently. He has had no treatment for eighteen months and is back at work.

The reappearance of chronic rheumatism in a patient appears to be of very favourable prognosis. But before diagnosing rheumatism, it is necessary to make sure that the suspected rheumatism is not due to bony or neural metastasis. A rheumatic subject loses his rheumatism as cancer develops, and may experience it again after removal of the growth by whatsoever method. This regression of rheumatism appears to be of value in dating the approximate onset of the neoplasm; but it is not absolute, as I have seen rheumatism return shortly after operation, in a case which recurred within six months. I have observed this alternation of rheumatism and cancer for about four years; up to the present I have had no cause to alter my opinion.

For those who wish to have more objective guides to prognosis certain laboratory tests are available; they are not necessary, but we apply them as routine. These tests are:—

1. *Blood Lipase, Rona Technique.*[1]—This lipase, not the so-called lipase of Shaw Mackenzie, tends to be high in cancer, but not invariably. We have used this test in every case since 1927 and find that a lowering level is usually favourable, an increasing level usually a sign of advance in growth.

2. *Blood Cytology.*—An increase, absolute, not relative, of small lymphocytes and eosinophil cells is also favourable. It is regarded as evidence of reactivity, which is favourable, but it does not imply that the reactability will be adequate to cause complete inhibition of the growth. On the other hand, absence of this finding practically always means that no response to treatment is taking place.

3. *Blister Test.*—A standard size cantharides blister, about one inch (but provided the size is always the same it does not matter), is applied between elbow and shoulder the night before inspection. The next day the fluid is removed if a take has occurred, the amount is roughly estimated, and a cell-count is made. This is regarded as a test of the reactivity of the patient's tissues to a standard irritation; the finding of a good take, with increase of endothelial, lymphocyte, and eosinophil cells, is also favourable with the limitations given under blood cytology. Increase of epithelial cells is not of any importance.

Duration of Treatment in Unfavourable Cases.—The duration of treatment for cases responding favourably has already been given. In a case apparently not responding I go on until the patient is definitely moribund, even though all the prognostics are bad, for occasionally a patient will begin to improve in the end. Example:—

Ken.—Carcinoma of rectum, sent by Mr. A. Jackman. Previous excision with radium application afterwards. Recurred, and pelvis reported full of neoplasm. For six months this man appeared to be steadily going downhill and all the tests were adverse; lymphocytes, etc., did not rise, blister result was bad, blood lipase increased from 13 to 21 per cent, and he appeared likely to die soon. Yet, on continuing, he began slowly to improve, and he was discharged nearly two years ago; he is back at work as a bricklayer.

THE RESULTS OF TREATMENT.

The results are dated from May, 1931, at which time the treatment as described was started. SSe had been given before this date, but R.A.S. and alternation only started then. The first series is from May, 1931, to September, 1932. The second series started 1932 and continues to the present time. Series 1 consists of 93 cases. No selection of any sort was applied to this series—every patient was accepted if there was room. In Series 2, as has been noted, the patient has to undertake to attend weekly for a year or more, and those of feeble mentality, not judged able to co-operate, are excluded. Series 1 (*see Table I*) includes 7 cases which had been treated on the earlier system, but, being not satisfactory, were given the present treatment; this

Table I.—Results in Series 1.

Name Index	Duration of Treatment	Type of Growth	Toilet
Failures (29 cases).—	Months		
Arn. ..	12	Mammary	Yes
All. ..	24	Mammary	Yes
Bes. ..	10	Ovarian	Yes
Bon. ..	19	Rectum	Colostomy
Bri. ..	4	Œsophagus	No
Bra. ..	16	Rectum	Colostomy
Car. ..	4	Bronchial	No
Cai. ..	4	Rectum	Colostomy
Edm. ..	5	Polymorph-cell sarcoma	No
Gay. ..	5	Lymphosarcoma	No
God. ..	7	Carcinoma of tonsil	No
Hal. ..	12	Osteosarcoma	No
Hob. ..	7	Mammary	No
Hil. ..	8	Prostate	No
Han. ..	5	Penis	No
Ile. ..	11	Seminoma	No
Jew. ..	5	Rectum	Colostomy
Jon. ..	7	Mammary	?
Ket. ..	3	Bronchial	No
Mil. ..	5	Sarcoma of pelvis	No
Mon. ..	6	Sarcoma, retroperitoneal	No
Phe. ..	11	Mammary	Yes
Pea. ..	9	Rectum	Colostomy
Tom. ..	30	Mammary	No
Tur. ..	9	Rectum	Colostomy
Tra. ..	6	Ovarian	No
Tur. ..	4	Rectum	Colostomy
Wat. ..	3	Labia majora	No
Tur. ..	4	Rectum	Colostomy
Still on Treatment (5 cases).—			
Har. ..	33	Rectum	Stationary
Hal. ..	30	Mammary	Very good
Han. ..	16	Myeloid leukæmia	Doubtful
Par. ..	19	Carcinoma of tongue	Bad
Sma. ..	48	Mammary	Good

Dropped Out (18 cases).—Very similar in types to those above. Five were doing well.

Inadequate Treatment (25 cases).—Types similar except one gastric carcinoma. Average duration of treatment 6 weeks.

Name Index	Duration of Apparent Cure	Type of Growth	Cause of Death
Deaths from Other Causes (3 cases).—			
	Months		
Bar. ..	5	Luteoma	Accident
Car. ..	18	Mammary	Influenza
Hew. ..	12	Mammary	Influenza
Cases of Apparent Cure (15 cases).—			
			Toilet
Bat. ..	18	Rodent	No
Dav. ..	15	Sarcoma of pubis	No
Eva. ..	15	Ovary	No
Gay. ..	20	Mammary	Yes
Hob. ..	19	Mammary	Yes
Ken. ..	17	Rectum	Colostomy
Mai. ..	15	Sarcoma of orbit	Enucleation of eye
Mos. ..	8	Ovarian	No
Par. ..	19	Sarcoma of ileum	No
Pie. ..	20	Ovarian	Yes
Phi. ..	7	Mammary	Yes
Phe. ..	7	Mammary	Yes
Ped. ..	7	Melanoma of eye	Enucleation
Sav. ..	18	Mammary	Yes
She. ..	6	Rodent of orbit	Enucleation

is why some of the durations of apparent cure almost approach the duration of the present method. Of these 93 cases, 18 dropped out, for the reasons noted under the present selection—i.e., stupidity, or distance, or expense; 5 of these cases were doing well and some of them stopped because they thought they were cured. Then 5 other cases are still receiving treatment; of these, 2 are doing well and are likely to be discharged later. Excluding these cases there are left 70 to which treatment has been given.

Of this series of 70 cases, 23 had quite inadequate treatment, the average duration being only six weeks; that is, they were extremely advanced cases which would not have been accepted if any selection had been made. If they are excluded, there remain 47 cases in which treatment has been adequate; in 29 cases treatment has failed, in the end, and all are dead. This leaves 18 cases, of which 15 are discharged as apparent cures. Then 3 cases, apparent cures, have died from influenza in two instances and street accident in one, in which autopsy disclosed no growth.

That is, of the whole series, apparent cure has resulted in 20 per cent. Excluding the cases still on treatment and those which gave up, the figure rises to 26 per cent. If only the cases which received adequate treatment are counted, the figure rises to 38 per cent.

Series 2, or those treated since September, 1932, is more difficult to assess; there are 62 cases (*see Table II*). Selection has been made, but only as regards mentality and ability to attend. Of these cases 12 have started treatment too recently for any decision to be made. Then, in spite of the selection, 7 cases dropped out; one was doing reasonably well. Inadequately treated cases number 15, average duration of treatment being four weeks. This leaves 28 cases to which adequate treatment has been given. Of these,

12 are dead, 4 are still receiving treatment, but are doing badly; 9 are doing well, amongst them being several who are being observed prior to discharge; 3 cases have been discharged as apparent cures. That is, the results are at least as good as in the first series.

Table II.—Results in Series 2.

Name Index	Duration of Treatment	Type of Growth	Toilet
Recently started on Treatment (12 cases).			
Stopped Treatment against Advice (7 cases; 1 doing well).			
Received Inadequate Treatment, Average Duration, Four Weeks (15 cases).			
Received Adequate Treatment: but Dead (12 cases).—			
	Months		
Bon. ..	9	Mammary	Yes.
Bri. ..	3	Carcinoma of uterus	No
Cra. ..	3	Carcinoma of tongue	No
Hol. ..	10	Mammary	Yes
Jon. ..	9	Mammary	?
Mea. ..	10	Ovarian	No
Poo. ..	7	Buccal carcinoma	No
Par. ..	4	Ovarian	No
Sen. ..	7	Mammary	Yes
Swi. ..	24	Mammary, bilateral	Yes
Sle. ..	7	Branchial	No
Tud. ..	10	Ovarian	No
Received Adequate Treatment, still Alive, but Doing Badly (4 cases).—			
Edw. ..	6	Primary, hepatic	No
Ham. ..	5	Œsophagus	No
Sam. ..	4	Œsophagus	No
Web. ..	5	Tonsil	No
Received Adequate Treatment, Doing Well (9 cases).—			
Bry. ..	16	Melanoma of eye	Enucleation
Bur. ..	5	Osteosarcoma	No
Bis. ..	4	Mammary	Yes
Fow. ..	8	Mammary	No
Poo. ..	14	Mammary	Yes
Sea. ..	5	Multiple myeloma	No
Tar. ..	11	Mammary	No
Tan. ..	8	Mammary	Yes
Wes. ..	13	Ovarian	Yes
Discharged, Apparent Cure (3 cases).—			
	Duration of Apparent Cure		
	Months		
Hem. ..	3	Mammary	Yes
Sti. ..	11	Osteosarcoma	Yes
Wil. ..	3	Mammary	Yes

These bald figures do not give quite a true picture of the results, for many of the cases recorded as failures showed some good result. For instance, amongst those who dropped out was this case:—

Hor.—This patient was seen by many, including the radium commissioners, for she was treated in the radium ward, owing to scarcity of beds. She showed on

admission a fungating septic breast with large glands in the axilla and over the clavicles. Her liver was an enormous craggy mass. Her lungs showed large masses in both sides and she had a spontaneous fracture of one femur. She was in early cachexia. 'Toilet' was done to breast, and she was then treated as I have described. She steadily improved, the fracture healed with 3 in. of shortening, the liver masses disappeared, the lung masses became no longer visible, and the only sign of disease left was a right supraclavicular mass, which appeared to be calcified. She got up, and went home, being able to walk with a limp. She attended for a time and was seen by Mr. Hey Groves, who advised surgical boots. She received from him the impression that she was quite cured, and nothing would persuade her to attend for further treatment. She was rather poor and had to attend in a hired car from her home thirty miles away. She did well for about six months, then relapsed and died.

Another case recorded as a failure was the following:—

Swi.—On admission this patient had a foul fungation of the right breast and a large central carcinoma of the left; there were many axillary and supraclavicular glands. She was much wasted and very anæmic from sepsis and hæmorrhage; she had been bedridden for some time. Mr. H. Chitty did a 'toilet' to both sides, and then she was put on the D4S system, as she lived in the Midlands. She did well for six months and went home, living fairly comfortably and able to do some work, quite as much as her advanced age allowed. Eight months later a small recurremce appeared about the scar, so she came to Bristol and was started on ionization, of which she had a full course; this appeared to arrest growth and she returned home and again received D4S. She was well for about six months, when again recurrence appeared. She returned to Bristol and had another course of ionization, after which she was again comfortable. The later history is that recurrences re-appeared and she would not again attend for treatment. A failure, but a dying woman was given about eighteen months of relatively happy and useful life.

Many similar cases could be recorded of temporary improvement amongst the failures. I will not labour the factor of relief from pain, but it is pronounced in many of the patients.

This is the new method, described as fully as possible. The work is done in public and has been inspected by a number of distinguished surgeons. The method has produced these results. If the same results are not obtained at other clinics, then let those clinics look to their technique and their ability to drive a difficult treatment through to results as good as, or, I hope, better than, these.

Lastly, and with great appreciation, I have to thank the other members of the team and the radiological staff for their help. Some have contributed more than others, but all have done their best; for that reason I think it would be invidious to single out workers by name, with the exception of Mr. E. Lloyd, M.P.S., to whose ingenuity and knowledge of chemistry the perfection of these preparations is due. The cost of this work has been borne by the Bristol Royal Infirmary Cancer Research Fund; a small grant has recently been made by the Imperial Cancer Research Fund.

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BILHARZIA DISEASE IN ENGLAND:
THE CYSTOSCOPIC APPEARANCE OF THE BILHARZIA BLADDER BEFORE AND AFTER INTRAVENOUS INJECTIONS OF SODIUM ANTIMONY TARTRATE.

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THE case now under review was a young man, M. S., aged 20. He had landed perfectly fit in Cape Town in February, 1929. Thence he proceeded to Mapunga, seventy miles north of Salisbury in Southern Rhodesia, to work on a tobacco estate, and whilst so occupied he had bathed frequently in a tributary of the Mazoe River—an auxiliary of the Zambezi.

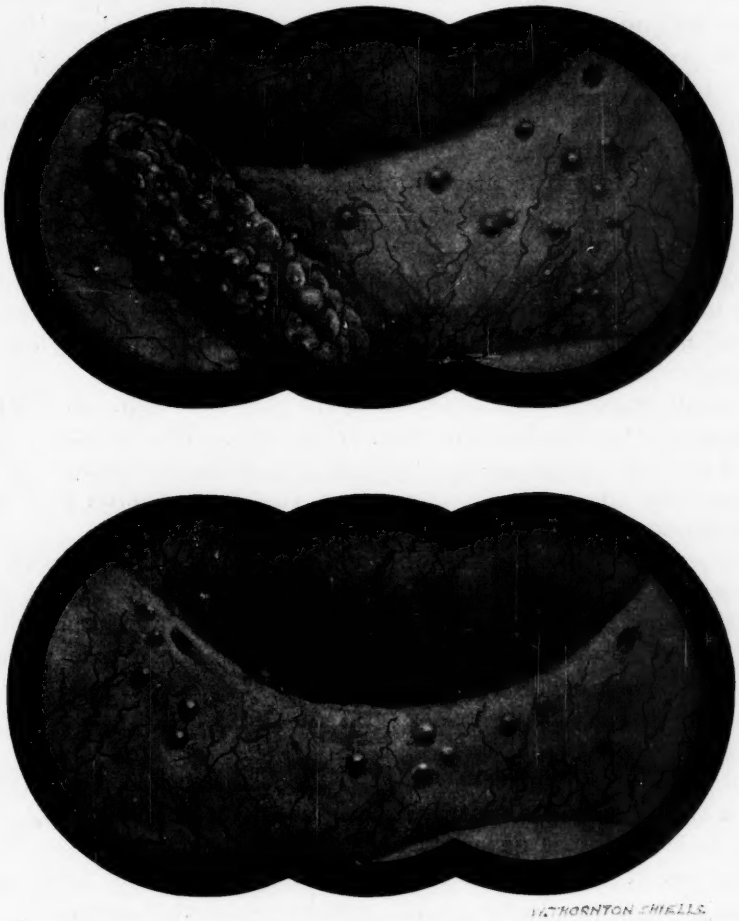
He appears to have contracted dysentery and bilharzia disease in June, 1929, and was admitted to the local hospital. During his illness his temperature rose to 104°, he passed several small clots of blood in his urine, and once had retention of urine for thirty-six hours. Quite unaware that he was suffering from bilharzia infection he returned home to England in November, 1929.

During the period June, 1929, to October, 1930, several attacks of hæmaturia occurred, some of which were considerable and were accompanied by the passage of clots, though all were of short duration. He also suffered from attacks of pain in both loins, one of which immediately followed a severe jolting on a tractor. On the whole the pain was worse in the left posterior renal angle than on the right side. In February, 1930, a cystoscopy and a left pyelogram were carried out, and the patient was told that they revealed nothing abnormal.

He was first seen by one of us (R. O. W.) on Oct. 10, 1930, and ova of *Schistosoma hæmatobium* were discovered in the urine on Oct. 16 by Dr. Cuthbert Dukes. The urine was slightly turbid, acid, specific gravity 1024, and contained terminal spined ova, though not in great numbers; these were found to be viable. Pus and blood were also present; no organisms were seen in films, but some streptococci and staphylococci were cultured. The results of blood examination are discussed later. A cystoscopic examination was made at this time, and *Fig.* 394 shows the local condition which was disclosed.

The bladder was almost normal except for the changes depicted, though a slight degree of congestion of the mucosa was present. The outstanding feature was the intense bullous œdema which surrounded the right ureteric orifice and extended on to the trigone below it. Amongst this œdema and

elsewhere on the trigone were vesicles, quite distinct from those bullæ, which are characteristic of a simple œdema in that they were of a peculiar yellow colour. Their presence is diagnostic of vesical bilharzia. Around the ureteric orifice were several small hæmorrhagic extravasations of recent origin; the opening of the ureter itself could just be recognized. The left ureter was not quite normal, being somewhat rigid and appearing to be in a state of chronic inflammation.



FIGS. 394, 395.—Bilharzia disease of the bladder before treatment, and one month after treatment with sodium antimony tartrate. The yellow nodules in *Fig.* 395 are the dead ova working their way through into the bladder cavity. They do not indicate active bilharzia disease.

A course of intravenous injections of sodium antimony tartrate was begun on Oct. 23, 1930, starting with ½ gr. and 1 gr. on the following day. The following injections were given on alternate days, the dose increasing ½ gr. each injection till 2 gr. was reached, then seven doses of 2 gr. each were given, and finally four doses of 2½ gr.—a total of 28 gr. in twenty-eight days (four injections were made each week, excepting one week, when three were given); the patient remained in bed on injection days. The complications

which occurred during the injections were the customary painful dry cough accompanied by pain in the chest and a feeling of discomfort in the throat immediately after the antimony injection. After a few days, in order to prevent this, the patient was given ¼ gr. of omnopon (intramuscularly) ten minutes before the antimony injection. This was successful in abolishing the cough, the pain in the chest, and the discomfort in the throat—formidable inconveniences of antimony tartrate injections. He complained of a feeling of sickness in the evening once after the injection, but beyond those mentioned there was no complication during treatment. He escaped the muscular pains, often paralysing in their severity, which frequently accompany antimony tartrate injections and are particularly liable to follow the larger doses. Possibly this was due to the administration of omnopon. As usual after a total of 9 gr. sodium antimony tartrate had been administered, ova and blood disappeared from the urine, and neither have reappeared in the specimens subsequently investigated at intervals over a period of three years.

The pulse-rate was taken before and five minutes after each injection, and the blood-pressure was also registered before and after the injections. This is not usually done, but investigations of pulse and blood-pressure during the course of injections yield valuable information on the depressing effects of antimony tartrate injections and constitute a useful control.

The second cystoscopic examination was made on Jan. 23, 1931, nominally one month after the last injection (*Fig.* 395). The bilharzia tissue had disappeared and the mucous membrane of the bladder appeared to be quite normal except for the small circular yellow vesicles scattered here and there like amber beads.

The patient was kept under observation after treatment and was last seen as recently as June, 1933, three years after the course of antimony tartrate, when he was working on his own farm in Northumberland, in normal good health, free from all urinary symptoms since the course of injections.

DISCUSSION.

A course of approximately 30 gr. of antimony tartrate, given intravenously in the dose and at intervals originally recommended by one of us (J. B. C.[1]) in 1918, is the generally accepted treatment of choice for human bilharzia disease in all its forms; the sodium salt is usually preferred to the potassium. The course of four or five weeks is somewhat long, but, provided the full course of 28 to 30 gr. (adult) can be given within that time. the cure is almost unfailing.

Antimony tartrate administered for bilharzia should be given in increasing daily doses for the first four days until 2 gr. per dose has been reached, then on alternate days 2 or 2½ gr., the aim being to reach as rapidly as possible the concentration of antimony in the blood necessary for the parasiticidal effect. Given timidly in too small doses, or given at too long intervals, antimony fails to produce the lethal effect on the parasites, the more resistant of which have a tendency to become antimony-fast.

A young man recently seen by one of us in London had contracted schistosomiasis (*S. japonicum*) near Shanghai whilst bathing in a tributary of

the Yangtze-kiang River. He was admitted into the local hospital and given a course of emetine. This was followed by a course of neo-stibosan (a pentavalent synthetic antimony derivative). When these failed there followed three separate courses of fouadin, the first of which was a modified course. Fouadin is neo-antimosan (Bayer), a trivalent synthetic antimony derivative. This not having the desired effect, a course of sodium antimony tartrate or tartar emetic was given. When he landed in England his fæces still contained scanty living ova, no doubt owing to the fact that some of the worms had become antimony-fast, the most powerful *bilharziacide* not having been used early enough nor according to the generally accepted technique.

Organic Preparations of Antimony and Bilharzia Disease.—Chemists searching for a compound producing the maximum parasito-tropic and the minimum organo-tropic effects in bilharzia have introduced neo-stibosan—an amino compound of antimony—a comparatively non-toxic pentavalent substance—effective in the protozoal infection leishmaniasis. When tried for bilharziasis neo-stibosan failed and was abandoned. Pentavalent organic preparations of antimony are not sufficiently parasito-tropic for the metazoal parasite bilharzia.

The trivalent Bayer preparation neo-antimosan (sodium antimony pyrocatechin di-sulphonate) named fouadin—after King Fouad of Egypt—has been tried since 1928. It is recommended by medical authorities in Egypt, but it has not altogether justified the praise of its Egyptian sponsors. Recent letters from South Africa report hepatic complications and loss of weight following the injections of fouadin for bilharzia. Fouadin is given by intramuscular injections and it is a useful drug for children whose veins are small, and for adults when antimony tartrate is contra-indicated.

Sodium and potassium antimony tartrate are in my opinion (J. B. C.) the parasiticides of choice for all cases of bilharziasis when it is possible to use them and when not contra-indicated.

The blood-picture in the present case was that of anæmia associated with eosinophilia: Hæmoglobin 72 per cent, colour index 0·9, eosinophils (before injections) 7 per cent. Two days after the completion of the injections the eosinophils were 12 per cent. Two months later eosinophils were 2 per cent, and five months after the completion of the course the differential count was normal: Polymorphonuclears 63 per cent, lymphocytes 31 per cent, large mononuclears 2 per cent, eosinophils 3 per cent, basophils 1 per cent.

The differential blood-count in bilharzia is of very definite clinical value—eosinophils may reach 70 per cent. Bilharzia and trichinosis amongst tropical diseases give the highest eosinophilia. Eosinophilia, however, has no relation to the number of parasites present—it registers the effort of the organism to combat the parasite. Eosinophilia increases as injections proceed. Eosinophilia three months after the termination of antimony injections argues the patient uncured.

In *Fig.* 395 the small round yellow vesicles like small canary seeds or the halves of small amber beads stand out on the clean mucosa with no surrounding inflammation. In *Fig.* 394 these nodules have the same general characters, but some of them are accompanied by slight inflammation. We do not consider them to indicate activity due to living ova; on the contrary

we believe that they are caused by the existence of ova which are dead, and which will ultimately be shed into the bladder cavity, for they are seen to be present after complete and successful treatment. We think this observation worthy of record.

We have already called attention to the clinical importance of the differential blood-count in cases of bilharzia disease.

There is illustrated in this case a third point—small, though one of considerable therapeutic importance in the clinical treatment of this disease. The distressing useless painful cough, and discomfort in the throat and chest, experienced immediately after individual injections may be alleviated or abolished by $\frac{1}{4}$ gr. of omnopon given ten minutes before injections. Possibly also the painful, alarming, paralysing muscular symptoms which occur later in the course may be eliminated by the same means.

Bilharzia disease—schistosomiasis—is not endemic in this country. There is on record no well-established case of the disease having been contracted in the British Isles. Bilharzia, however, not infrequently crops up in England, but is always imported. Biologically it would not appear impossible for the disease to thrive and to pass from one person to another in England. There are stretches of fresh water, e.g., at Frensham and Fleet in Surrey, and in other localities, where soldiers bathe whilst at home from abroad in water which harbours species of snails, which, given the opportunity, might function as the necessary intermediate hosts; but there are few days in the year when the miracidium in the ovum would hatch out and survive in the free state and infect the snails. The British climate preserves the country from endemic bilharzia disease. The cases which are seen in England come from the Far East—China, Japan, Formosa (*Schistosoma japonicum*), from Egypt or one of the many infected areas in Africa, from Palestine, Mesopotamia (*Schist. hæmatobium* and *mansoni*), or the West Indies (*Schist. mansoni*), and an occasional case (*Schist. mansoni*) from South America. Owing to increasing facilities for travel and trade, bilharzia disease is not an uncommon visitor to this country, though usually it does not occur in a serious form.

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SPINDLE-CELLED MESENTERIC TUMOURS: WITH REMARKS ON SIMILAR RETROPERITONEAL TUMOURS.

By H. A. PHILLIPS, Melbourne.

Definition.—Modifying Twistington Higgins and Lloyd,[1] who wrote on mesenteric cysts, it would seem advisable to define a 'mesenteric' tumour as one which occurs as a primary growth in or near the mesentery and which has not originated in a normal retroperitoneal organ or gland. It is proposed to call these 'paramesenteric tumours', and such tumours will therefore embrace: (1) Those of the retroperitoneal tissues; (2) Those growing from the connective tissues between the leaves of any of the peritoneal folds, omenta and mesenteries.* Confusingly enough, the cyst described by the above authors as mesenteric was in point of fact, retroperitoneal. The reason for the necessity of a term which will include both retroperitoneal and mesenteric tumours and cysts is obvious: (1) These structures have a common anatomical relationship to the peritoneum—they are all subperitoneal; (2) The same theories of developmental origin are applicable to them; (3) The actual pathology of solid tumours, as will be shown below, is similar.

Historical.—It appears that whilst Benevieni was the first to report a mesenteric cyst (sixteenth century), Morgagni (1761) was the first to note a solid mesenteric tumour, although this distinction is often given to Portal (1803). Hertzog[2] in 1897 collected from the literature the first series of reported cases (57). Vance[3] in 1906 added a further list of 27 cases. In the British literature, Greer[4] in 1911 records a series of 33 cases of fibromatous tumours culled from various sources. In the German, Szenes[5] has analysed a series of 60 cases (1918). The most recent account is given by Rankin and Major.[6]

Now there has been no little confusion and much repetition in this literature of solid tumours. In some cases lymphomatous and carcinomatous tumours have not been excluded; cases have been duplicated into several series, and the histology and pathological genesis of the tumours have received scanty notice, American authors in particular contenting themselves with a discussion of the clinical features. Probably the best modern series is that of Rankin and Major.[6] It comprises 22 mesenteric tumours of the Mayo Clinic, 7 of these being cysts and 15 solid tumours. No tumour of lymphatic-gland origin entered into the series. This excellent review, though, like many of its predecessors, gives no after-histories of its cases and is content to follow the older terminology.

* The extra-ligamentous broad ligament tumours are tacitly excluded, as their pathology is so closely bound up with that of the uterus and ovary. No doubt, however, an analogy exists between the fibromata and myomata of this region and the paramesenteric tumours here discussed.

Incidence.—To show how rare these tumours are, and to compare their incidence with that of other paramesenteric lesions, the following figures are given. Of the last 4500 autopsies performed at the Alfred Hospital, Melbourne (since 1914), there were :—

1 case of tumour of the gastro-hepatic ligament.*
3 cases of retroperitoneal sarcoma.*
1 case of adrenal neuroblastoma.
3 cases of retroperitoneal hydatid.
6 cases of Hodgkin's disease showing large retroperitoneal glandular enlargements as a prominent feature.
4 cases of lymphosarcoma of the aortic and lumbar glands.
2 cases of retroperitoneal hæmatoma due to ruptured aortic aneurysm.

Unfortunately a similar résumé of the in-patients who did not come to post-mortem in this thirty-year span cannot be included. But of the 19,788 in-patients admitted from 1930–3 there were :—

4 cases of retroperitoneal tumour—proved by operation.*
1 case of tumour of the great omentum—proved by operation.*

Curiously enough there is no record of a single case of mesenteric or retroperitoneal cyst.

The Museum of the Royal College of Surgeons has only two specimens of mesenteric tumour, the one a fibroma and the other a lipoma (Nos. 6151–1 and 6155–2).

There is no mention in the literature of any percentage of incidence of mesenteric or retroperitoneal tumour.

Résumés of the clinical features of the cases noted above, followed in each instance by the descriptive pathology and after-history, are given below. It will be shown that, despite their variation in site, these tumours have a common pathology.

'MESENTERIC' TUMOURS.

Case 1.—**Tumour of gastro-hepatic ligament.**

C. J., female, aged 63, and multiparous. She had noticed a swelling in the abdomen for four years. In the last three months it had caused her a little discomfort and she was definitely more dyspnœic and pale than previously and had grown weaker.

On Examination.—This tumour was found to be a hard, spherical, immobile mass dull to percussion and without fluid thrill. The flanks were resonant. The tumour filled the abdomen and was palpable per vaginam, where a small atrophic uterus was pushed back by it. A diagnosis of ovarian cyst was made with some misgivings, and a laparotomy was performed by the honorary gynæcologist.

Operation.—About a pint of free fluid escaped on opening the abdomen, and the tumour was found to be cystic in one place; after the aspiration of a pint of brownish fluid the tumour could be eventrated, when it became evident that there

* Seven of the nine cases marked above with an asterisk form the basis of this paper. Two cases of retroperitoneal sarcomata were not included, because there was no microscopic section for one, and the other was microscopically a round-celled tumour and regarded as possibly of lymphatic-gland origin. It is very important in these cases, if possible, to identify the lymph-glands as normal.

was no ovarian pedicle. It was necessary to strip the upper pole from the posterior wall of the stomach, during which the latter was inadvertently opened, there being no covering peritoneum visible. The tear was quickly repaired and a pedicle defined in the depths of the abdomen. This was hastily ligated, the tumour removed, and the abdomen closed as the patient's condition had become rather alarming. She died twenty-four hours later from post-operative shock.

AUTOPSY.—At post-mortem the uterus and adnexa were normal, and it was definitely established that the tumour had developed in the gastro-hepatic ligament and that the pedicle contained hypertrophied branches of the gastroduodenal and right gastric arteries. There was no other tumour in any other part of the abdomen or in the thorax or brain. The tumour originating in the gastric border of the gastro-hepatic ligament extended in such a way as to obliterate the lesser omental sac, pushing the stomach forwards and upwards and the transverse colon posteriorly, remaining 'peritonealized', however, on all surfaces except that in contact with the stomach, and being also enclosed by the outer two layers of the attenuated great omentum, somewhat distorted by adhesions.*

PATHOLOGY.—Macroscopically the tumour was ovoid, 30 cm. (12 in.) in length and 17·5 cm. (7 in.) in breadth and depth. It weighed 4196 grm. (9 lb. 4 oz.). Its surface was greyish-white and was covered with peritoneum except at the region of the pedicle, where it was irregular and particularly cystic (*Fig.* 396).

FIG. 396.—*Case* 1. Macroscopic appearance of tumour.

In cross-section most of the central portion of the tumour consisted of soft yellowish caseous material into which passed bands of firmer fibrous tissue. There was a cortex of about 5 cm. in width which in some parts could be described as fleshy, but in others appeared more like fibrous tissue. A few small cysts were visible in the fibrous areas.

Microscopically the bulk of the tumour was composed of structureless caseous material taking up the counterstain. Many areas of the tumour consisted of bundles of spindle cells with very few intervening fibres of connective tissue demonstrable by van Gieson's staining (*Fig.* 397). Many of these cells possess nuclei which stand out as long rods with blunt ends (*Fig.* 398), resembling therein unstriated muscle fibres of embryonic type. They stain brown with van Gieson's. Other areas consist mostly of myxomatous tissue with a few of these spindle cells interspersed amongst it. There are visible several dilated spaces lined with endothelium and resembling lymphangiomatous tissue. The small cysts visible macroscopically had no lining membrane. They are therefore probably degenerative.

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* McW. Millar[7] has reported a similarly situated tumour which he terms a " pedunculated extra-gastric leiomyoma of stomach with hæmorrhagic degeneration ". It would appear to resemble in pathology the spindle-celled tumours described in this paper.

The biopsy section of the pedicle tissue still remaining in the gastro-hepatic ligament was found to show similar microscopic findings. The tumour was considered to be a fibromyxomyoma or mixed tumour of embryonal type.

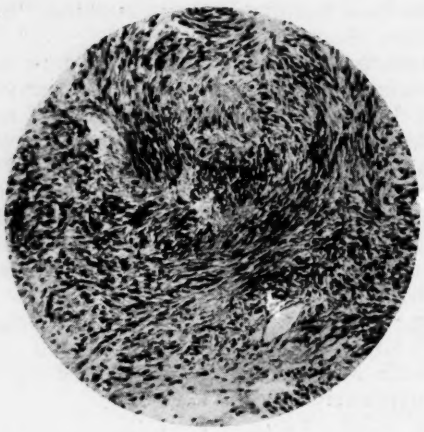

FIG. 397.—*Case* 1. Microscopic appearance of tumour showing spindle cells.

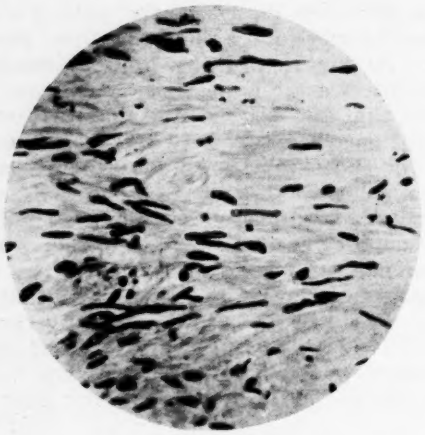

FIG. 398.—*Case* 1. Section showing nuclei.

Case 2.—**Tumour of great omentum.**

H. P., female, aged 73. She had noticed a lump in the right iliac fossa for four months. It became larger, till at the time of examination it filled the abdomen. She complained of slight loss of weight and mild indigestion, but nothing else of importance.

ON EXAMINATION.—There was a large, spherical, hard tumour the size of a human head filling up the lower abdomen. The flanks were resonant, and pelvic examination revealed nothing untoward. The tumour was immobile. Examination of the blood indicated a secondary anæmia, there being 65 per cent of hæmoglobin, 4,130,000 erythrocytes per cmm., and considerable anisocytosis in the stained film.

OPERATION.—At operation the tumour was found to be in the layers of the great omentum but very adherent to surrounding structures. It was considered unwise to remove it, so a portion was excised for section and the abdomen closed.

The patient had an uninterrupted convalescence and was discharged fifteen days later. She died eight weeks later, no post-mortem examination having been made.

HISTOLOGY.—Histologically the greater part of the section consisted of myxomatous tissue in which there were numerous areas showing various degrees of necrosis and hæmorrhage. There was at the periphery of the tumour a cortex 3 or 4 mm. wide of much more cellular tissue consisting of irregularly arranged spindle and oval cells in a fibrillar matrix. There were no muscle fibres though the cells stained brown with van Gieson's, and no blood spaces of sarcoma type.

It appears probable that in the more central portions the tumour was undergoing an ischæmic form of myxomatous degeneration even to the point of caseation. The microscopic appearances, taken into consideration with the short clinical history, would suggest a diagnosis of degenerating fibroma.

RETROPERITONEAL TUMOURS.

The following are the case histories and pathology of four similar spindle-celled retroperitoneal tumours.

Case 3.—**Pedunculated tumour of retroperitoneal pouch.**

P. R., male, aged 50. For ten years this man had noticed a tumour in his lower abdomen. It had occasioned him no discomfort, and over most of that period

did not seem to be enlarging. However, for the last two years he had been troubled by a frequency of micturition, sometimes two-hourly, through the day and night. There were no symptoms referable to the bowel and the patient had not lost weight.

On Examination.—There was an easily palpable oval mass lying across the lower abdomen and occupying both iliac fossæ. A distended bladder could be made out anterior to the tumour, and the presence of small bowel also anterior was suggested by a resonant percussion note over the upper half of the mass. Per rectum the tumour appeared to be lying in the pelvis, pressing against the outer wall of the rectum, though not attached to it. Bimanually it was freely mobile and non-fluctuant, and its surface felt hard and irregular.

Operation.—At operation it was discovered to be a retroperitoneal solid tumour growing between the bladder and rectum and bulging forwards to become pedunculated. The peritoneum and pelvic fascia over the narrowest part of the

Fig. 399.—*Case* 3. Macroscopic appearance of tumour.

tumour was incised and the tumour shelled out. There was slight hæmorrhage from the cavity remaining, but this was easily controlled by pressure. The abdomen was drained for twenty-four hours.

The patient made an uneventful recovery, and all his symptoms, including the frequency of micturition, entirely disappeared.

Two years later the abdomen was opened again for the relief of intestinal obstruction due to adhesions, and no recurrence was discovered. The patient was alive and well one year after this second operation.

Pathology.—The tumour when removed weighed 1730 grm. (3 lb. 11 oz.). It was 25 cm. (10 in.) in length, and 15 cm. (6 in.) in breadth and depth. It was clothed in peritoneum except at the base (*Fig.* 399), where there were some irregular cystic projections.

On section it was solid and greyish-white in appearance. It possessed a thick capsule and was intersected by numerous trabeculæ of fibrous tissue enclosing gelatinous areas into some of which hæmorrhage had occurred.

Microscopically the tumour was also very similar to that of *Cases* 1 and 2. It consisted of a myxomatous tissue with varying admixtures of spindle cells. The cysts are degenerative in type, and have no lining membrane. There were no fully formed blood-vessels to be seen, but collections of erythrocytes were occasionally present in spaces lined by a single layer of endothelial cells. The inadequacy and immaturity of the blood-vessels is a common feature of this type of tumour, and explains the ease with which degeneration and caseation occurs.

Case 4.—**Retroperitoneal sarcoma of left lumbar region.**

H. W., male, aged 42. Twelve months previously his left leg had started to swell; at first only in the evenings, but later it became continuous and extended up the leg. For one month he had noticed his abdomen swelling. There was no alteration in his bowel or micturition history, but there had been some loss of weight.

On Examination.—The abdomen was distended. The swelling was due to the presence of free fluid, distended bowel, and of a large mass mostly on the left side. Both flanks were dull, but there was a band of resonance immediately to the right of the tumour.

There was a moderate degree of anæmia. Numerous investigations were carried out and paracentesis was performed, a gallon of fluid being removed. Eventually a laparotomy was performed.

Operation.—At the operation much free fluid escaped and the tumour was found to be a retroperitoneal growth. When needled a large quantity was removed. When incised the tumour was very hæmorrhagic; the bleeding area demanded packing. The tumour was too extensive for removal.

About three weeks later the wound broke down and a fæcal fistula developed. The patient gradually went downhill, and died three months later.

Autopsy.—At the autopsy the whole of the small intestine was found to be pushed to the right, the ascending and transverse colon to be grossly dilated, and the descending colon to be completely flattened out over a large tumour growing from the left lumbar region. A small fæcal fistula connected the descending colon with the abdominal wall, and communicated with a necrotic cavity in the tumour. Extensive peritonitis had obviously extended from this site. Widespread adhesions needed separation before the tumour, the size of a pumpkin, could be removed. There were smaller tumours the size of walnuts in the adjacent tissues.

The liver, kidney, and adrenals were normal. There was a small adrenal rest 2 in. below the right kidney; the bladder and prostate were normal, and the abdominal lymph-glands were not involved. The thorax and cranial cavities were normal.

The actual cause of death was peritonitis and intestinal obstruction.

Pathology.—Macroscopically the tumour when removed measured 38 cm. × 30 cm. × 20 cm. and weighed 22 lb.* On section it was homogeneously solid except for a few cysts of about 1 cm. in diameter and the necrotic cavity communicating with the bowel. The tumour tissue was white, soft, and arranged in large lobules. There were a few irregular areas of hæmorrhage. The structure of the outrunner growths was similar.

Fig. 400.—*Case* 4. Microscopic appearance of tumour, showing granulation of nuclei.

Microscopically the sections consist almost entirely of irregularly directed fasciculi of regularly arranged large spindle cells which are separated by a minimum of fibrils. The nuclei of the cells are plump and oval, almost filling the cell bodies. They are distinctly variable in size and chromicity, are granulated (*Fig.* 400), and often show nucleoli, centrosomes, and mitotic figures. There is an occasional giant cell of tumour type.

Blood-vessels are scanty and are represented by blood spaces, most of which have a lining of a single layer of endothelial cells.

On the fasciculation and whorling, the shape of the nuclei, and the sparseness of the connective tissue, the diagnosis of myoma was made. With rather more

* The largest yet reported is a fibroma of 25 lb.[8]

fibrous tissue, the resemblance to uterine fibroids would be very close. No cross-striation could be demonstrated in the protoplasm.

The great variation in the size of cell and the mitotic activity of the nuclei together with the immaturity of this very cellular muscle tissue would indicate that degree of malignancy which was evidenced by the autopsy findings.

This tumour is therefore regarded as a leiomyosarcoma. It is possibly because the tumour is myomatous rather than sarcomatous that the malignancy is of local type only, the usual spindle-celled sarcoma of this size in other parts of the body generally having blood-stream metastases.

Case 5.—**Retroperitoneal tumour of left iliac fossa.**

S. E., female, aged 65. For about four months the patient had noticed a gradual increase in size of her abdomen. For two days she had suffered constant gnawing pain which radiated over the whole abdomen and was accompanied by nausea and much flatulence. The bowels had opened normally. Twelve months previously hysterectomy had been performed for a fibroid, which, though degenerating, was non-malignant by microscopy.

On Examination.—There was a large rounded mass palpable in the left iliac fossa. It was mobile and appeared to be attached by a pedicle rising from the pelvis. The tumour was dull to percussion and extended across the mid-line to the right side. The flanks were resonant and vaginal examination elicited nothing of importance.

Operation.—Though the nature of the tumour was not known, the abdomen was opened through a lower left paramedian incision for the relief of intestinal obstruction. A large gelatinous mass was found rising from the left side of the pelvis. The exact pedicle could not be ascertained as the tumour 'came away' in soft masses with much bleeding. However, as much of the tumour as possible was removed in this piecemeal fashion with some smaller masses in the omentum. There was very little free fluid, and the intestine was not obstructed.

The wound healed, and after a course of deep X-ray treatment the patient was discharged 'improved'. Six months later her condition was much worse and she was unable to report for treatment. Six months after this she could not be traced, so death had probably supervened.

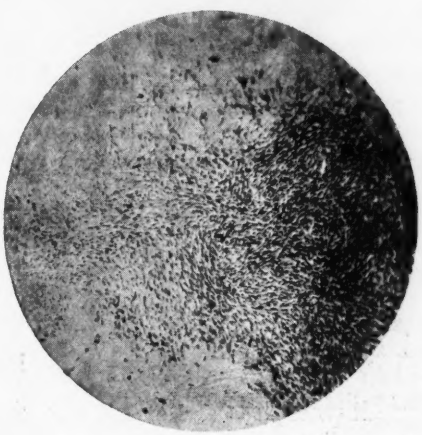

Fig. 401.—*Case* 5.
Microscopic appearance of tumour.

Histology.—In the main, the appearance of the microscopic section of this tumour (*Fig.* 401) is identical with that of *Case* 4. Most of the tissue is just as cellular, but there are numerous areas of necrosis into several of which extensive hæmorrhage has occurred. There was no cystic development. The cells were not quite as atypical and giant cells were rare. This tumour is also regarded as a leiomyosarcoma.

Case 6.—**Lumbar retroperitoneal tumour.**

M. B., female, aged 64. For four months this patient had suffered dull epigastric pain, worse at night, but unaccompanied by vomiting, nausea, dysuria, or other symptoms. She herself felt the tumour in her abdomen.

On Examination.—There was a hard, nodular, immobile mass in the epigastrium the size of a fœtal head. Examination of the blood revealed a secondary anæmia.

Operation.—At operation through a right upper paramedian incision a large smooth vascular tumour presented. It rose from the posterior abdominal wall and

extended from diaphragm to pelvis, pushing the pancreas and root of mesentery forward. As it was considered inoperable, a portion was excised for section and the abdomen closed.

The patient was discharged improved, and a course of deep X-ray therapy arranged. This patient was not improved by the deep radiation and died within two months of operation.

HISTOLOGY.—At first sight the microscopic appearance of this tumour differs somewhat from that of the others. There are many areas of fat and other areas of tumour tissue in which the cells are much smaller, and the fasciculation is not as definite as in the foregoing tumours. However, there are some areas where the reticulum is arranged in layers and the spindle shape of the cells is visible (*Fig.* 402). Transition from this to the more haphazard arrangement of small ovoid or polyhedral cells in a network of collagen and elastic fibres can be traced.

FIG. 402.—*Case* 6.
Microscopic appearance of the tumour.

The nuclei of the typical cells have pointed ends and are probably fibroblasts, so that the tumour may be regarded on morphological grounds as a fibroma rather than a myoma. It is, however, very difficult to distinguish microscopically a fibromyoma from a cellular fibroma of this type, as the young cell bodies of a cellular fibroma have practically the same staining qualities as the myoma cells. Embryologically in fact they are almost identical cells.

The fatty areas probably represent the remains of the subperitoneal fat, as the section taken at operation could only be from the periphery. They may, however, be neoplastic, when the tumour could be better regarded as a mixed tumour of mesoblastic elements.

The fact that there are no grossly atypical cells as appear in sections of *Cases* 4 and 5 gives the impression that the tumour is not rapidly growing, though the growing edge shows the infiltration of local malignancy.

DISCUSSION.

Rather less than half the cases in the literature of mesenteric tumours are malignant and are referred to as sarcomata, fibrosarcomata, myxosarcomata, myosarcomata, or liposarcomata. Of the benign form, the lipoma is the commonest 'pure' tumour, and fibromas are quoted as the rarest,[9] though probably a pure myoma is the rarest. 'Mixed' tumours, however, occur much more frequently than pure tumours—all combinations of fibro-, lipo-, myxo-, myo-, and even chondro- being employed to designate the tumour.[10] Whilst most of the fibromyomata are of the leio- type, a rhabdo- type has also been described.[11]

In this nomenclature, the mesenteric tumours above may be termed a 'fibromyxomyoma' (*Case* 1), and a 'fibromyxoma' (*Case* 2). The retroperitoneal tumours comprise: 1 fibromyxoma, 2 leiomyosarcomata (*Cases* 4 and 5), and 1 fibrosarcoma (*Case* 6). Yet there are identical appearances in some part or other of each by microscopy—compare *Figs.* 397, 401, and 402.

They may be collectively described as spindle-cell tumours, but it would appear that they are really of the type of tumour known as 'mixed'. This, however, is rather a loose term. 'Mixed' parotid tumours, for example, have now been crystallized into epithelial tumours with metaplasias and degenerations and carcinomatous potentialities, and the tumours of this series can be similarly regarded as of one type of original spindle mesoblastic cell with analogous degenerations and metaplasias, and sarcomatous potentialities.

In fact, developing the theme further, it seems that a gradation of embryonal tumours exists. The original embryonic cells were totipotent, but as development and specialization occurred, cells lost certain potencies and became only multipotent and later unipotent. If one could postulate a stranding of these cells in embryonic life in paramesenteric situations with later recrudescence, then a totipotent *Anlage* would produce a teratoma or tridermal tumour; a very multipotent one a bidermal dermoid (e.g., hypoblast and epiblast); a less multipotent one a 'mixed' tumour of one layer only (e.g., a dermoid with epiblastic tissues only, or a mixed paramesenteric tumour with mesoblastic derivature only); and the unipotent one would produce the ordinary simple tumours that we know as fibroma, lipoma, or myoma. Malignancy may supervene at any stage of the evolutionary history of these Rip Van Winkle cells, and the teratoma or mixed tumour or simple tumour become malignant. Tourneux[12] is of opinion that many of the benign paramesenteric tumours become sarcomatous—a belief well borne out by the histological appearances of the above tumours, and the incidence of sarcoma in the literature of this type of growth.

The following case is of a retroperitoneal tumour which must have been frankly sarcomatous from the outset. It is not a spindle-celled or mixed tumour, but is included to show the great variation which may occur when extreme malignancy is the feature, fortunately rarely, of these tumours.

Case 7.—**Retroperitoneal sarcoma with metastases.**

I. W., female, aged 41. There was a history of six weeks' pain in the left iliac fossa and left thigh. There had been amenorrhœa for four months. During the last six weeks multiple subcutaneous nodules had appeared over trunk and limbs, and the patient became weak and emaciated. In the last two days she had complained of severe occipital headache and vomited continuously.

On Examination.—The patient was very ill, but apart from the subcutaneous nodules little could be ascertained. No tumour was palpable in the abdomen. There were no neurological phenomena elicited. The patient died two days after admission.

Autopsy.—There were about fourteen of these subcutaneous nodules, and the largest was 1 cm. in diameter. There were numerous small nodules about 4 mm. in diameter scattered through the lung, and several larger ones in the retroperitoneum and omentum. The largest of these was 5 cm. in diameter and overlay the left psoas muscle. The pancreas and liver, spleen, kidneys, adrenals, and intestines were normal. The uterus was carefully examined but was normal. There was a similar tumour in the cerebellum and other smaller ones in the cerebrum.

The ribs, skull, lumbar vertebræ, and sternum were sectioned but were normal, as were the other bones of the skeleton.

Histology.—The tissue consists of masses of tumour cells in no definite arrangement. A very fine reticulum or fibrillar mesh separates the individual cells, and in some places there are isolated strands of connective tissue. The cells themselves are exceptionally anaplastic. Most of them are irregularly polyhedral in outline, but not a few are ovoid. The nuclei show excessive mitotic activity.

All degrees from the single immature cell, through the larger more immature cell, to the immature syncytial giant cell formations are well shown (*Fig.* 403). All this betokens a high degree of malignancy which is not belied by the widespread blood-stream metastases, which the autopsy showed to be present in brain, subcutaneous tissues, and omentum. Local infiltration can be seen at the periphery of the tumour. Owing no doubt to the rapidity of growth, necrosis occurs in the most ischæmic situations, so that some areas show a peritheliomatous arrangement of tumour cells around the open blood spaces. The vessels are poorly developed and there is a considerable extravasation of blood into the least cellular areas.

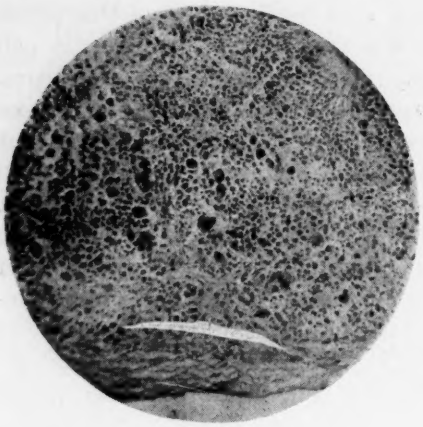

FIG. 403.—*Case* 7.
Microscopic appearance of tumour.

The structure of the tumour strongly recalls that of giant-cell tumours of bone, tendon-sheaths, and other mesoblastic tissues, which tumours, be it remembered, whilst generally innocent, may assume malignant characters and metastasize by the blood-stream. There were no tumours in the bony skeleton in this case. The tumour must be regarded as a pure paramesenteric sarcoma, which is so much more anaplastic and malignant than the ordinary spindle-celled sarcoma that it has almost lost its spindle characteristics and the 'mixed-cell' appearance.

The low grade of malignancy of the tumours can be explained by the lateness of its supervention. They are locally infiltrative, though not to the same degree that carcinomata are; and would probably recur if not completely removed. The earlier the malignancy develops, the more rapidly does local infiltration occur. Metastasis by the blood-stream is also possible then. Case 20 of the Mayo Series of mesenteric tumours[6] had secondaries in the liver, and *Case* 7 of the above series had secondaries in the brain and subcutaneous tissue, and, as can be seen from the anaplasia of the microscopic section, must have been malignant from the outset.

Actual teratomata, though rare, have been reported[13]—even chorioma.[14] So also have dermoids.[15] All the 'double-barrelled' spindle-celled tumours reported above now fall into one pathological group which can still be called 'mixed' tumours.

It is interesting to note at this juncture that similar mixed tumours,[16] and dermoids, occur in the mediastinum. The original mesenchyme which formed both paramesenteric and mediastinal connective tissues was a happy hunting ground for the early multipotent cells.

One point that arises out of the above is that when dealing with apparently simple tumours, e.g., fibroma or lipoma, it must be remembered that other mesoblastic elements may be present unnoticed in but a cursory pathological examination. Many apparently simple lipomata when removed show fibromatous or sarcomatous tissue in perhaps one spot only,[17] and the infiltrating edges of some simple lipomata can be explained only by the presence of these areas.

There are described other paramesenteric tumours whose appearances are suggestive of a primitive intestinal or renal origin. Most of these, though

not all, are by virtue of their glandular structure cystic. MacAuley[18] reported a series of ileocæcal cysts thought to be enterocystomata, and Higgins and Lloyd[1] report a 'mesenteric' cyst thought to be a pararenal one derived from Wolffian body remains. Some, too, are thought to arise from Müllerian body remains or ovarian rests, and these too are naturally cystic.[19]

In recent American literature it is wondered whether mesenteric myomata or fibromyomata are not derived from primitive muscle cells which have wandered away from the uterus or broad ligament. This is not so, of course, as these tumours may occur in the male. Nor do they arise from misplaced cells of the ligament of Treitz or the pelvic fascia; they arise *in situ* from multipotent cells. This question is well dealt with by Carter.[15]

Classification of True Paramesenteric Tumours.—One is now in a position to formulate a classification of paramesenteric tumours which may be used both clinically and pathologically:—

BENIGN.—*A. Simple*: Lipoma, Fibroma, Myoma.
B. Embryonal.
1. Teratomatous.
2. Dermoid.
3. Mixed (*Cases* 1, 2, 3).
4. Developmental—
   a. Intestinal.
   b. Wolffian.
   c. Müllerian.

MALIGNANT.—*A. Simple*: Sarcoma (*Case* 7).
B. Embryonal.
1. Teratomatous—
   a. Sarcoma.
   b. Carcinoma.
2. Sarcoma arising in mixed tumours (*Cases* 4, 5, and 6).

This classification may also be applied to paramesenteric cysts. The older classification of these cysts was into serous, chylous, sanguineous, echinococcal, and dermoid varieties, and the most recent (Ewing's) into chylous, enteric, nephrogenic, and dermoid.

Serous cysts are degenerative: they may be seen developing in the caseous and myxomatous areas of the tumours of *Cases* 1, 2, and 3 above. The chylous cysts are of similar causation probably, and the sanguineous ones are hæmatomata only. So that all these may be put in the simple group. Ewing's enteric, nephrogenic, and dermoid cysts then fit the embryonal group of the above classification.

It is not impossible that a certain number of paramesenteric cysts may arise by degenerative processes liquefying the centres of such ill-nourished tumours as that of *Case* 2.

Theories of Origin of Paramesenteric Tumours.—These may be briefly tabulated: (1) At one time they were supposed to be a form of extra-uterine pregnancy—later it was discovered the tumour could develop in the male! (2) Theory of fœtal inclusions—the tumours were compared with parasitic monsters! (3) Theory of parthenogenesis. (4) Theory of heterotopsy and cell rests. (5) The embryonal theory as expounded above. The last theory

seems to afford the most satisfactory explanation of the pathological nature and behaviour of the tumours.

Signs and Symptoms: Differential Diagnosis: Treatment: Prognosis.—These questions, while not unimportant, are not as intriguing as the pathology, and have been satisfactorily dealt with by other writers.

The tumours seem somewhat more frequent in the female; Pakowski[20] puts the ratio at 70 per cent, and in this series the proportion is 5 females to 2 males. The sexes were equal in the Mayo Series. They may occur at any age, though the malignant ones develop generally after 40.

Signs and Symptoms.—The initial symptom complained of is either the presence of the tumour itself or the onset of a complication: whether the tumour be mesenteric or retroperitoneal, the commonest complications are: (1) Intestinal obstruction; (2) Urinary symptoms; (3) Torsion and degeneration with or without hæmorrhage into the degenerated area.

Of the above 7 cases, 4 noticed the tumour and attributed vague pain to it, 1 complained of urinary symptoms, 1 of swelling of the leg the result of pressure on the iliac veins, and 1 of secondaries in the skin. One case developed intestinal obstruction and a fæcal fistula later.

The shortness of history, rapidity of growth, and the presence of secondaries or ascites are suggestive of malignancy. In all the cases there was a definite grade of secondary anæmia present.

The actual signs of the tumour must depend on its site and nature. As a general rule mesenteric tumours are mobile, but neither of the two reported here was—they were too large and adherent. The retroperitoneal ones are generally fixed, but one of these reported above (*Case* 3) was ballottable in the pelvis as it was pedunculated. They may be solid or fluctuant. The flanks are resonant unless a secondary ascites or intestinal obstruction be present.

Diagnosis.—The differential diagnosis is a question of exclusion diagnosis: cysts and tumours of other organs in the region of the tumour must be eliminated clinically or with the help of pyelogram, cholecystogram, and barium meal or clysma. The blood should be examined for evidence of leukæmia, the Casoni and complement-fixation tests performed for hydatid elimination, Wassermann reaction taken, and Hodgkin's disease excluded.

It should be noted that in ordinary experience the commonest cause of a spherical hard abdominal tumour which can be moved into any quadrant of the abdomen of an adult over 20 is not generally a mesenteric cyst or tumour but a carcinoma of the colon, or, less commonly, calcified mesenteric glands.

Exploration is advisable, as complications and malignancy occur, and in any case pre-operative diagnosis is always a little uncertain.

Treatment.—The tumour should be excised if this is possible. If its relationship to other structures such as the pancreas or intestinal blood-vessels is too intimate, or there is too much infiltration, there is nothing further to be done. In excising a tumour in the mesentery of the bowel, the circulation of the corresponding loop must be observed. Resection is often necessary.

In inoperable cases deep X-ray therapy may be tried. In *Cases* 5 and 6 above there was no improvement whatsoever with deep X-ray. This affords

a striking contrast to the behaviour of lymphosarcoma under deep X-ray treatment.

Prognosis.—In the matter of prognosis, which has not been fully discussed by previous writers, the following points emerge: (1) Only about one-third of these tumours can be removed at operation; in this series 3 out of 7 were removed. (2) The immediate mortality rate is about 40 per cent.[21] (3) When removed completely, the prognosis is good once the patient gets over the shock; however, only one case in this series of 7 is alive three years after operation. (4) An idea of the malignancy of the tumour may be obtained from a study of the histological appearance of a section and a prognosis given on that. (5) Deep X-ray treatment does not improve the prognosis.

CONCLUSIONS.

1. A series of 2 solid mesenteric tumours and 4 retroperitoneal tumours are reported. They are classed together as paramesenteric tumours.
2. The similarity of their pathology is discussed and their embryonal origin suggested.
3. A classification is put forward suitable for both solid and cystic tumours.
4. The signs, symptoms, diagnosis, treatment (including X-ray), and prognosis are briefly discussed.

I am indebted to the honorary surgical staff of the Alfred Hospital for permission to publish these cases.

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OBSERVATIONS ON PLEURAL ABSORPTION.*

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THE mortality of the so-called post-pneumonic, usually pneumococcal, type of empyema is with even moderate skill in treatment a low one. In the so-called syn-pneumonic type, which is usually streptococcal in origin, the state of affairs is quite different, and it is generally accepted that even with the most skilful treatment the mortality rate is rarely less than 10 per cent, and, depending upon the severity of the particular epidemic, frequently higher. It is true that in many cases of this type death actually occurs from some concurrent major condition such as septicæmia, pneumonia with abscess formation, or meningitis, and that the empyema may be merely an incident in the course of an overwhelming general infection, but there can also be little doubt that the presence of a suppurative inflammation of such a large serous membrane as the pleura must have a seriously adverse effect on the course of the illness. Just as it is a mistake to attribute the whole of a patient's desperate condition to the suppurative pleurisy while the presence of an extensive underlying pneumonia is overlooked, so is it a mistake to overlook the fact that the additional burden of an indifferently treated pyothorax may turn the balance against the patient.

In spite of this admitted persistent high mortality, no new suggestions for treatment have been made during the last fifteen years—that is, since the recommendation of aspiration in the early formative stage and postponement of rib resection until the pneumonic condition has subsided. It is clear that before any logical improvement in treatment can be suggested it is essential to know more of the underlying physiological and pathological processes taking place in the pleura, and of these processes it seems that of first importance is absorption. Absorption from this large serous membrane must be the main feature causing the illness resulting from its infection. This illness arises partly from the absorption of bacterial and other toxins and partly from absorption and dissemination of micro-organisms themselves. There is ample experimental and other evidence to show that bacteria are freely absorbed from the pleura into the general circulation. Wadsworth,[1] Corfer,[2] Higgins and Lemon,[3] and other workers have all shown that particulate matter such as carmine and indian ink or bacteria is readily absorbed. Thus Higgins and Lemon,[4] after studying the results of injection of finely-divided graphite particles, state: "The sternal and the tracheal lymph nodes were always densely black within one hour. It was obvious, then, that the lymph drainage occurred promptly and that free particulate matter was

* Read at a meeting of the Association of Surgeons in Manchester, May, 1933.

distributed into the lymph nodes together with that contained within the phagocytic cells both of the polymorphonuclear and the monocytic types. Furthermore it appeared that the material absorbed and transferred through the lymphatics reached the thoracic duct or the right lymphatic duct and emptied into the venous circulation within a period of approximately one hour; it thus became possible for such particulate material to reach the systemic circulation and to appear in the liver, spleen and bone-marrow within a relatively short time after injection. . . . Within two to three hours of the injection the Kupffer cells were swollen to several times their original size, and they encroached on the lumen of the sinusoids, or desquamated into the lumen. This appearance always preceded the recognition of particulate matter within them." This proves quite definitely that an open pathway exists for particulate matter from the pleura into the general blood-stream.

It is to be noted that no attempt is made in this paper to add further arguments to the discussion that exists as to the relative parts played by the lymphatic system and blood-vessels in the removal of exudate from the pleura. The generally accepted view is probably the correct one—namely, that removal of particulate material, including bacteria, takes place by way of the lymphatics, and soluble material by way of the blood-stream. Starling's work[5] seems to prove this latter completely, and the work of the other investigators already mentioned amply supports the former. It is probably not out of place to draw a comparison with an infection of the cellular tissues of the hand or fingers; the infection may remain strictly localized with but minor symptoms of general disturbance from toxæmia; or it may spread to the axillary lymph-glands, with or without an obvious lymphangitis; or it may lead to general blood-stream infection with great prostration or death of the patient. It is not suggested that in every case of pyogenic infection of the pleura general dissemination of micro-organisms takes place; it is clearly the function of the lymphatic system to seize, and if possible fix, the invading bacteria, and there is but little doubt that this fixation in the lymph-vessels and lymph-nodes of the mediastinum[3] is successful in the majority of cases, just as all but very few infections of the cellular tissue of the hand are effectively prevented from spreading beyond the axillary lymph-nodes. No one will deny, however, that when the pleura is infected there is a much greater tendency for general blood-stream infection to occur, either on account of low resistance on the part of the patient (e.g., infants) or of unusual virulence on the part of the infecting organism (e.g., epidemics). For the purpose of this paper it is taken for granted that the absorption of the purulent fluid is harmful; and it is also implied that while soluble toxins can be absorbed, so can micro-organisms. Indeed, one of the aspects which it is wished to stress is that this absorption of bacteria and toxins from the infected pleura may be the most prominent feature in the causation of the secondary—septicæmic—manifestations from which death so often occurs.

Although, as already mentioned, much work has been done on the absorption of particulate matter from the pleura, almost no investigations have been made into the factors governing the absorption of fluids by the pleura, except for some observations by Starling, Leathes, and Tubby[5, 6] nearly

forty years ago. This is the more remarkable when one considers the important part the pleura plays in practical medicine and surgery.

The animals used in my investigations were rabbits. These have the disadvantage of possessing a relatively small chest as compared with the dog, but the conditions in the rabbit's chest are much more comparable to those in the human owing to the more stable and relatively impermeable mediastinum it possesses, whereas the dog's mediastinum readily allows passage of air and fluids from one side of the chest to the other. The experiments were conducted under intravenous nembutal anæsthesia, a method of great value in observations on the respiratory apparatus seeing that one is able to eliminate the difficulties associated with inhalation anæsthesia. The general plan has been to introduce fluid into the chest by means of a fine cannula from a burette, and at the end of the experiment to open the chest and suck out the remaining fluid, which was then measured in the same burette.

ABSORPTION FROM THE UNINFLAMED PLEURA.

The simplest fact that has been ascertained is, as could almost have been predicted, that the rate of absorption of fluid, i.e., normal saline, varies directly with the volume of fluid present. Thus, it is slow with a few cubic centimetres of fluid and rapidly increases as the volume grows larger. *Table I* shows the increase of rate of absorption of normal saline (1) with increase of volume of fluid in the chest, (2) with increased depth of respiratory movements.

Table I.—Showing Increase of Rate of Absorption of Normal Saline.

Volume of Fluid	Volume Absorbed	
	Shallow Respiration	Deep Respiration
c.c. 20	c.c. 0·75	c.c. 3·0
50	4·25	7·5
75	7·50	10·5
100	7·25	14·0

This is also shown by the varying times of survival of animals after the intrapleural injection of varying quantities of a strychnine solution in normal saline. Thus, if a solution is made up containing a lethal dose in 5 c.c. of fluid and only 5 c.c. are introduced into the pleura, death does not occur before some twelve hours. On the other hand if 50 c.c. of the same strength solution are given, death occurs much more rapidly—in fact in two hours.

The importance of variation in the respiratory movements has next been studied, and the results are striking. An account of some initial experiments on this aspect of the importance of the respiratory movements was published in an earlier paper,[7] but since then fuller investigations have been made.

With quiet respiration the rate of absorption is moderate; as the respiratory movements become deeper and more laboured (for example, following the

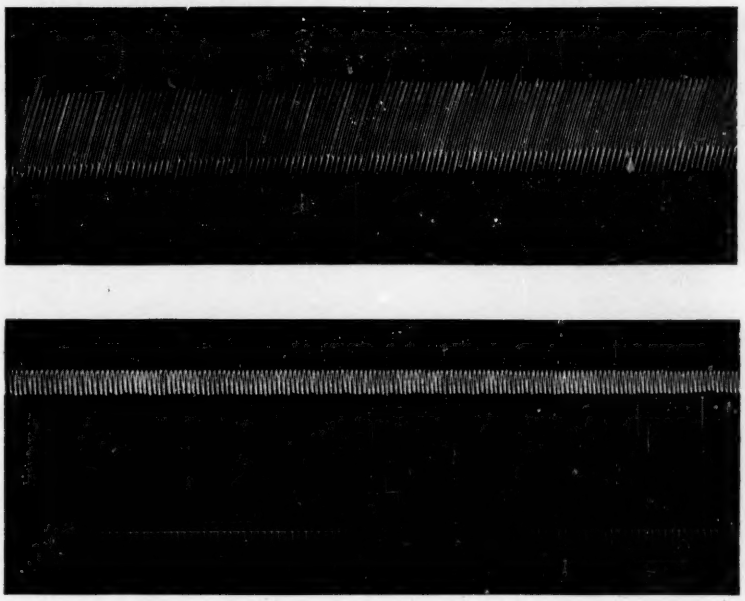

FIG. 404.—Tracings of respiratory movements from two rabbits after the introduction of 50 c.c. of normal saline into the pleura. The animal breathing deeply (A) absorbed 9·6 c.c. in one hour; the one breathing quietly (B) absorbed only 5 c.c. in the same time.

administration of CO_2 or partial occlusion of the trachea) the rate of absorption increases. *Table I* shows this quite clearly and also shows the variation in the absorption rate with variation of the volume of fluid in contact with the pleura. (*See also Fig.* 404.)

In other words, if a small amount of fluid is in the chest and respiration is not embarrassed, very little absorption takes place. If, however, a maximal amount of fluid is present and respiration is laboured and deep, then absorption occurs at a surprisingly rapid rate. This is even better shown in the dog when an animal with 200 c.c. of saline in the pleura and breathing quietly absorbed 15 c.c. in two hours, and a similar animal breathing forcefully absorbed 139 c.c. (*Fig.* 405).

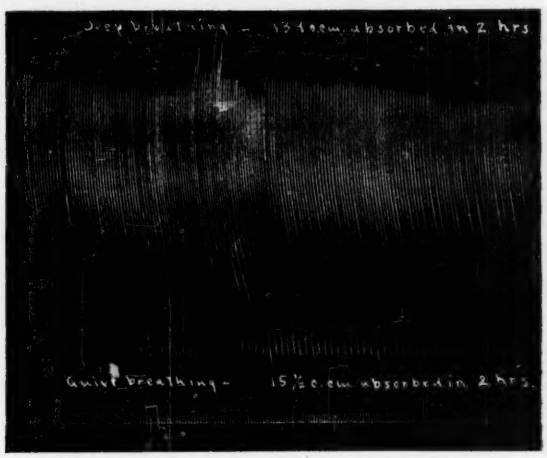

FIG. 405.—Simultaneous tracing from two dogs after the introduction of 200 c.c. of normal saline into the pleura. The animal breathing deeply (upper part of figure) absorbed 139 c.c. in 2 hours; the other animal, breathing quietly, absorbed only 15½ c.c. in the same time.

The importance of the respiratory movements can also be shown dramatically by comparing the survival time of two rabbits of the same litter after the introduction into the pleura of 50 c.c. of strychnine solution. A cannula in the opposite pleura connected with a tambour was used to give the record shown in *Fig.* 406. The animal which breathed quietly survived twice as long as the animal whose depth of respiration was increased by administering CO_2, and in each case on aspirating the fluid remaining in

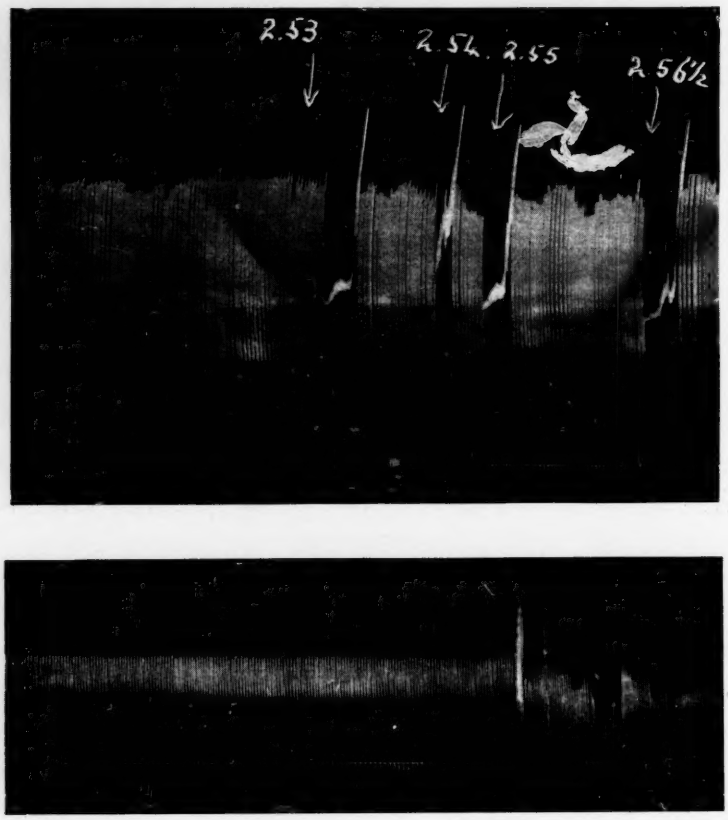

FIG. 406.—Tracings of respiratory movements from two rabbits of the same litter after introduction into the pleura of 50 c.c. of saline containing strychnine. The upper curve is from the one to which CO_2 was administered, and death occurred in 35 minutes. In the lower curve breathing is of average depth, and death did not occur before 55 minutes. The arrows pointing to interruptions in the tracings mark convulsions.

the chest it was found the approximate volume containing a lethal dose had been absorbed, i.e., 5·5 c.c. in the case of the animal breathing deeply, and 4·85 c.c. in the case of the other; this gives an hourly rate of 9 c.c. and 5·4 c.c. in each case. In a similar experiment with a weaker solution of strychnine the times of survival were 135 minutes with quiet respiration and 70 minutes with deep respiration.

The increased rate of absorption with greater volume of fluid probably results from the greater surface area in contact with the fluid. The increase

with deeper respiratory movements may, of course, be partly due to the greater agitation giving a wider surface of contact, but this cannot be the sole factor, and it is probable that the chief reason is that the increase of power in the respiratory pump causes a greatly increased circulation of both blood and lymph.

ABSORPTION FROM THE INFLAMED PLEURA.

The question that next arises is whether the absorption rate is at all modified by inflammation of the pleura. The only work having any direct bearing on the subject I have been able to discover is the observation by Starling[6] that the absorptive power of the pleura could in no way be affected either by scalding the lining with hot water or by treatment with sodium fluoride, and Corfer's experiment[2] on the removal of particulate matter following treatment of the pleura with dilute HCl, from which he concluded that the absorption rate is delayed.

Fluid accumulates in any serous cavity when the balance between the rate of formation and absorption is altered. No one will deny that when the pleura is inflamed fluid accumulates chiefly because it is formed at a greatly excessive rate. The result of the inflammation on the rate of absorption is, however, masked by this great outpouring of fluid, but a moment's consideration will show that it can either remain unaltered, can be diminished, or can be increased. It is, moreover, of considerable practical importance to know the exact change, if any, that takes place in the rate of absorption, and it is indeed a surprising fact that this question has so far been given such scant attention and that no one has attempted to settle the problem definitely. It has been accepted that absorption does occur, but whether at an increased, decreased, or unaltered rate is not known. Some, in fact, have gone so far as to suggest that no appreciable absorption can occur when exudation is occurring, for fluid can scarcely pass both ways to and from blood-vessels and lymphatics. This latter argument, however, entirely overlooks the phasic conditions resulting from the respiratory movements which undoubtedly play a very important part in absorption.

It was found that the simplest and most certain way of producing as it were a standard inflammation of the pleura was by the injection of a few minims of turpentine. Within twenty-four hours an intense sero-fibrinous reaction occurs with formation of a large effusion. If the injection is repeated after a day or two, this progresses to the stage of thick pus formation in a well-shut-off empyema cavity.

The problem that presents itself is the difficulty of accurately determining the volumetric absorption of fluid from a cavity into which exudation has occurred and is still occurring. It is clear that, however carefully one aspirates the chest dry at the beginning of the experiment, one can never be sure that some fluid is not left in (in fact one might say that one can be sure that some fluid will be left in) and also fluid is being formed at an unknown rate during the actual experiment. These difficulties have been circumvented, at any rate in part, by the use of a saline solution of strychnine containing a lethal dose of the drug in a known volume of the fluid. After

aspiration of the existing exudate this solution is injected into the pleura and the death of the animal gives a definite end-point. The fluid remaining at the end of the experiment is measured.

Using this method, the absorption rate has been estimated at stages of pleurisy ranging from twenty-four hours to eighteen days, and the results have been definite and constant in showing an increased rate of absorption. This increase is more marked in the earlier stages (twenty-four to forty-eight hours). *Table II* shows results from these experiments, and it can be seen that a control animal would survive 100 minutes with absorption of the requisite amount of fluid containing a lethal dose, while the animal with an inflamed pleura would survive only 35 minutes. Even in the third week the absorption rate is at least doubled.

Table II.—Showing Increased Rate of Absorption with Acute Inflammation and Increased Depth of Respiration.

Days of Inflamation	Time of Survival	Control
	Shallow Respiration	
	Mins.	Mins.
24 hours	35	100
3 days	25	180
4 days	53	180
10 days	60	135
15 days	69	120
	Deep Breathing	
24 hours	25	100
48 hours	15	135
5 days	40	180
18 days	25	120

The amount of fluid absorbed by the end of the experiment in the animals with an inflamed pleura varied, as one would expect, since it was not possible to be sure that one had aspirated all the exudate at the beginning of the experiment and fluid was also being formed during the whole course of the experiment. In spite of this, volumetric confirmation of the increased rate of absorption was frequently obtained in addition to the diminution in the time of survival. Thus :—

R. 47.—Control. Weight 2·6 kilos.
L.D. = 2·6 × 0·08 = 2·08 mgrm. (contained in 10 c.c.).
Strychnine solution used = 10 mgrm. in 50 c.c. of normal saline.
12 noon.—50 c.c. of fluid introduced into left pleura. Respiration (controlled by kymographic tracing), average depth.
1.40 p.m.—Death occurred; i.e., in 100 minutes.
Post-mortem.—13·25 c.c. absorbed, i.e., 7·8 c.c. per hour.

R. 48.—Twin of control. Weight 2·6 kilos.
Twenty hours' inflammation; other details identical with control.
2.54 p.m.—50 c.c. of solution introduced into left pleura. Respiration (kymographic tracing) comparable to that of control.
3.30 p.m.—Death occurred, i.e., in 36 minutes.

POST-MORTEM.—14·15 c.c. absorbed, i.e., 24 c.c. per hour. There was a typical diffuse pleurisy with much recent exudate extending over the whole of the left lung and left pleural space.

Comment.—Death occurred three times as quickly as in the control of the same litter and there was close verification in the volume of fluid removed (13·25 c.c. in R. 47, 14 c.c. in R. 48). In both cases, as in all others, the rapid onset of rigor mortis characteristic of strychnine poisoning occurred.

Again :—

R. 74.—Control. Weight 3 kilos.
L.D. = 2·4 mgrm., and this is contained in 12 c.c. of solution.
10.48 a.m.—50 c.c. of fluid introduced into left pleura.
12·44 p.m.—Death occurred, i.e., in 2 hours.
POST-MORTEM.—12·75 c.c. absorbed, i.e., 6·37 c.c. per hour.

R. 73.—Twin of control. Weight 2·9 kilos.
In this case turpentine was injected into the left pleura on two occasions and turbid fluid aspirated at frequent intervals until thick pus was obtained. The final experiment was carried out on the fifteenth day.
Aug. 3.—Aspiration of chest resulted in 32 c.c. of purulent fluid with thick flocculi.
11.13 a.m.—50 c.c. of fluid introduced into left pleura.
12.22 p.m.—Death occurred, i.e., in 69 minutes.
POST-MORTEM.—12 c.c. absorbed, i.e., 10·5 c.c. per hour. There was an intense diffuse pleurisy on the left. The right side of the chest was normal and contained no fluid.

Comment.—The shorter time of survival is confirmed almost exactly by the volumetric absorption.

Such striking confirmation was not always obtained, but there was never an excessive difference between the amount absorbed from the control and from the animal with the pleurisy, and the character of the fluid removed at the end of the experiment in the latter case always showed clear evidence of having been mixed with purulent exudate.

The same variation of rate of absorption with variation in respiratory movements was also shown to occur, i.e., if deep breathing was induced, the absorption rate was increased still further (*see Table II*)

There is an obvious criticism to this method—namely, that the animals die sooner because they are not well; i.e., the lethal dose for them is smaller than for a normal animal. Apart from the confirmatory evidence of the volume of fluid absorbed, as shown above, this objection can also be disproved in another way; if the solution is placed in the opposite, i.e., the healthy, side of the chest, it can be shown that the lethal dose and time of survival are the same as for a healthy animal.

Thus :—

R. 84.—Weight 3·05 kilos.
L.D. = $3{\cdot}05 \times 0{\cdot}8 = 2{\cdot}44$ mgrm. (= 12 c.c. of fluid).
July 30.—Injection of turpentine into left pleura (ether anæsthesia).
Aug. 3 (fourth day).—Aspiration of left pleura resulted in removal of 17 c.c. of turbid fluid.
11.45 a.m.—50 c.c. of fluid into *right* side of chest. Respiration of average depth.
3.20 p.m.—Death occurred, i.e., in 3 hours, 35 minutes.

POST-MORTEM.—14 c.c. of fluid absorbed from the right chest, i.e., 3 c.c. per hour. On the left side there was a diffuse acute pleurisy and 6 c.c. of turbid fluid were present, i.e., either this amount had not been removed at the preliminary aspiration, or it had formed during the course of the experiment, and in any case illustrates well how unsafe it would have been to rely on volumetric methods alone to estimate absorption from the inflamed side.

R. 95.—Weight 3·2 kilos.
Aug. 25.—Injection of turpentine into left chest.
Sept. 3.—Ninth day of pleurisy. Preliminary aspiration gave 35 c.c. of purulent fluid from the left pleura.
10.38 a.m.—50 c.c. of fluid into *right* chest. Respiration of moderate depth.
12.43 p.m.—Death occurred, i.e., in 125 minutes.
POST-MORTEM.—13·5 c.c. absorbed from right pleura (L.D. = 12·8 c.c.). Left pleura showed splendid example of suppurative pleurisy with 3 c.c. of fluid present.

It is not suggested that this strychnine method of estimating the absorption rate from the inflamed pleura is without fault. It is only intended to present the method, state the results obtained from it, and draw certain conclusions in view of the consistently similar results. It is felt that in the absence of a better method the observations are worthy of notice. Although in each case an approximate lethal dose has been worked out, it must be made quite clear that such an arbitrary dose alone is of no true scientific value; apart from other considerations, the weight of the animal may be inaccurate, e.g., from a recent meal or from rapid wasting. For this reason it has been a constant practice to use as a control an animal of the same litter which was also in apparent good health.

The objection that one is using a crystalloid toxic substance and not a colloidal one is more pertinent and is difficult to answer unless one has actually repeated the experiments with a colloidal toxin. To do this, however, would be no light task and would probably introduce other and more complicated sources of error. At the same time I should like to point out that when normal saline is introduced into the pleura, proteins are rapidly added to it, as shown by Starling,[5] and the absorption rate of this colloid-containing fluid continues unchanged. Some experiments were also carried out during this series in which rabbit's serum was introduced into the pleura instead of normal saline, and it was shown that the same variations of the absorption rate occur, although the whole process is slower with the serum than when normal saline is used.

From the experiments on the uninflamed pleura it was pointed out that a patient with a large effusion and breathing deeply is absorbing fluid from the pleura at a very rapid rate. From these observations in the presence of inflammation it is suggested that in a patient with an acutely inflamed pleura containing a large amount of free fluid and who is correspondingly dyspnœic (or even more grossly dyspnœic from an associated pneumonic process) the rate of absorption is grossly—in fact, one may even say alarmingly—increased. Just as these experimental animals with an acutely inflamed pleura and very dyspnœic killed themselves more quickly by means of the strychnine they absorbed, so it is suggested that the grossly dyspnœic, perhaps cyanosed, patient with a suppurative pleurisy is helping to kill himself more quickly by a more rapid absorption of toxins.

When one remembers the intense hyperæmia of acute inflammation, especially during the early stages, it is quite reasonable to suppose that such an increased rate of absorption does occur, and it is suggested that this increased vascularity is the mechanism responsible for the increase.

EFFECT OF PNEUMOTHORAX ON THE ABSORPTION RATE.

When this greatly increased rate of absorption became apparent the obvious step was to attempt to find some further means of diminishing the rate of absorption, and to this end the effect of artificial pneumothorax was investigated. Although there has been a great deal of work on the absorption of gases from an artificial pneumothorax, no attempt has been made to ascertain the effect of air replacement on the absorption of fluids from the pleura. It was expected and hoped that the absorption rate would be greatly diminished when air was added, but this was found not to be so. The rate of absorption was at least doubled. Thus, in *Table III*, the effect of a

Table III.— Showing Increase of Volume Absorbed with Addition of Air.

Air	Effect of Pneumothorax	
	Normal Saline	Volume Absorbed in 1 Hour
c.c.	c.c.	c.c.
0	25	0·25
45	25	3·25
50	25	3·75

pneumothorax on the volume of absorption is seen, and in *Tables IV* and *V* the effect on the time of survival after using a strychnine solution is illustrated. In these latter experiments the volumetric increase of fluid absorbed also corresponded. As the proportion of air increases so does the rate of

Table IV.

Air	Effect of Pneumothorax		
	Volume of Fluid	Time of Survival	Weight
c.c.	c.c.	Mins.	Kilos.
0	50	65	3·0
0	50	54	3·0
25	50	28	3·3
25	50	27	3·25
50	50	30	4·0

absorption. *Table V* shows that deep and laboured respiration further increases the rate of absorption. In other words, absorption takes place more rapidly from a hydropneumothorax than from a hydrothorax, and more

rapidly still when dyspnœa is present. Similarly, when inflammation is present the addition of air still further increases the rate of absorption (*Table VI*). A solution of strychnine in normal saline was employed in these experiments.

Table V.

Air	Effect of Pneumothorax		
	Volume of Fluid	Time of Survival	Weight
c.c.	c.c.	Mins.	Kilos.
0	25	180	3·0
10	25	110	2·95
15	25	95	2·7
20	25	88	3·0
25	25	80	3·0
25	25	68	3·45
40	25	66	3·2
50	25	65	3·3
50	25	51	3·15
70	25	38	3·6
Deep Breathing with CO_2			
25	25	33	3·2

Once more to recapitulate: the patient who is grossly dyspnœic with a large pyo-pneumothorax and an acutely inflamed pleura is absorbing harmful substances at an alarmingly rapid rate.

The explanation of this increased rate of absorption in the presence of a pneumothorax is difficult to see; it is the reverse of what one would expect, but the results of these observations are so striking and so consistent that only the one conclusion can be drawn from them. It may be stated here that all the series of experiments recorded in this paper have been confirmed at least two or three times, although to avoid confusion only the simplest outline of figures has been given.

Table VI.

Air	Effect of Pneumothorax and Inflammation			Remarks
	Volume of Fluid	Time of Survival	Weight	
c.c.	c.c.	Mins.	Kilos	
0	50	120	3·0	Control. No inflammation
0	50	73	3·25	Control. 24 hours' inflammation
25	50	50	3·25	Pneumothorax and 27 hours' inflammation

The only other experimental work on the effect of a pneumothorax on absorption from the pleura has been concerned with the fate of particulate matter (e.g., indian ink), and the somewhat meagre results are in direct conflict with those recorded above. Dolley and Wiese[8] conclude from observing the rate of flow from the thoracic duct that the rate of absorption of trypan blue from the pleura is delayed; they do not seem, however, to be acquainted with Starling's work[5] in which he showed that the removal of such a dye from the pleura occurs almost entirely by way of the blood-stream, and its appearance in the lymph from the thoracic duct can be accounted for by its filtration from the blood into the tissue spaces and thence into the lymphatic system secondarily. He showed, for instance, that it could be readily demonstrated in the urine at once; Dolley and Wiese make no mention of the urine examination, and one is forced to discount this part of their observations. The well-known experiments demonstrating the greater time taken for the removal of soot particles from the lung on the same side as a pneumothorax was present, although showing undoubted diminution of absorption from the lung, are not applicable to absorption from the pleura.

DISCUSSION.

The practical application of these findings is straightforward, and in pleural suppuration applies especially to the early, so-called formative, stage, when purulent fluid is first noticed in the chest but it has not thickened to form pure pus and the patient is still desperately ill from the accompanying pneumonic process or general infection. It is at this, the most dangerous, stage of the illness that refinements of detail of management of the effusion are lacking. It is clear that aspiration should be repeatedly practised to diminish the total volume of fluid, and all other possible measures taken to relieve dyspnœa. The frequency and need for aspiration I feel is a matter of first importance. At present it is a common practice to aspirate the fluid as often as appears necessary to relieve gross dyspnœa. This usually means fluid is allowed to accumulate for some forty-eight hours, or even longer, by which time the effusion is sufficiently large to cause gross displacement of the mediastinum. Removal of all this accumulated fluid at one aspiration is not only dangerous but frequently impossible owing to the symptoms of distress which rapidly develop, especially in little children. We know from these observations that such a patient has been absorbing toxic substances at an excessive rate; that he has been helping to kill himself more quickly just as the experimental animals did. It is certain that aspiration should be practised more often both to prevent accumulation and to give the maximum relief from dyspnœa. I feel that twice a day is not too often in a really ill patient, and this can be carried out with very little trouble if the step suggested by Tudor Edwards is followed. When the local anæsthetic is administered for the first aspiration a short incision is made down to the intercostal space, and after aspiration the small wound is packed and left open. Subsequent aspirations can be performed with very little disturbance to the patient and with but little fear of a spreading cellulitis of the chest wall.

In the acute stage in which absorption of exudate is not desirable, air replacement, if performed at all, should be minimal and only sufficient to relieve symptoms of distress following aspiration. If aspiration is repeated as often as recommended it is doubtful if symptoms of distress due to removal of fluid should occur. It as to be noted (*see Tables III* and *IV*) that if air is *added to* fluid in the chest, e.g., 25 c.c. of air added to 25 c.c. of fluid, the absorption rate is increased (survival time after strychnine diminished from 180 to 80 minutes). If, however, air is made to replace fluid in the chest, e.g., 50 c.c. of fluid half replaced by air, the absorption time is slightly diminished (survival time 65 minutes becomes 80 minutes). In other words, the *replacement* of fluid removed by a smaller quantity of air will do but little harm; *addition* of air, or replacement by a larger quantity, will hasten absorption.

There are times, however, when it is wished to assist absorption of an effusion, such as in some cases of clear effusion, and in certain selected cases of empyema. Replacement of the aspirated fluid by air will help absorption, and, where there is no contra-indication (e.g., tuberculosis) the administration of CO_2 at regular intervals will also help. The air replacement of pleural fluids is, of course, no new procedure. It has been strongly advocated by many as a means of treatment. These new observations do serve, however, to put the method on a sound physiological and pathological basis.

SUMMARY.

1. The necessity for a greater knowledge of the underlying physiological and pathological processes occurring in the pleura in acute inflammation is pointed out, and it is suggested that of these processes the most important is absorption.

2. From experimental observation it is demonstrated that absorption of fluid from the pleura varies directly with the volume of fluid present, and, moreover, is profoundly modified by variations in the depth of the respiratory movements. With deep breathing the rate is much increased over that when respiration is moderate or slow in depth.

3. Acute inflammation produces a marked increase in the rate of absorption of fluid.

4. The presence of air in the chest in addition to fluid still further increases the rate of absorption; if inflammation is present and the patient is dyspnœic, as in the case of a large pyo-pneumothorax, the rate of absorption is alarmingly increased.

5. Certain practical conclusions are drawn from these findings.

The greater part of this work was carried out by the writer as Surgical Research Scholar to the Association of Surgeons (1932–3); a smaller portion as the Astley Cooper Student, Guy's Hospital.

I wish to acknowledge with grateful thanks the facilities for work in the Department of Physiology, Guy's Hospital, accorded me by Professor M. S. Pembrey, and the very kind help and advice I received from him. *Fig.* 405 is published by permission of the Editor of the *Journal of Thoracic Surgery.*

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THE PLAN OF THE VISCERAL NERVES IN THE LUMBAR AND SACRAL OUTFLOWS OF THE AUTONOMIC NERVOUS SYSTEM.

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For some years past surgeons have displayed great interest in the sympathetic nervous system. Papers dealing with the subject from different aspects have been published in astonishing numbers. It was soon apparent that many of the authors had not a sound conception of the anatomy and physiology of the system, and that the nomenclature was not all that could be desired. Many facts which had been discovered long ago by physiologists were re-discovered by surgeons, and not always did the latter appear to know of or acknowledge the work of the former. The conclusions of distinguished physiologists have been attacked by surgeons who thought that they had discovered facts hitherto unknown, although a careful search through the literature would have shown that the physiologists concerned were not ignorant of the facts and that they had not neglected them in drawing their conclusions. Sweeping assumptions have been made from quite insufficient and ill-established observations.

In connection with the autonomic nervous system an immense amount of careful detailed work has been done by physiologists, who succeeded years ago in presenting a fairly definite though incomplete plan of the nerves. J. N. Langley in particular stands out as a gifted and devoted worker in this field.

For a detailed description of the nerves dealt with in this paper, as seen in cats and rabbits, the reader is referred to a paper by Langley and Anderson.[1]

On the other hand, anatomists have lagged behind, the descriptions given in most text-books leaving the reader with no notion whatever of any ordered plan. The nomenclature of the anatomists is chaotic, and takes but little account of that used by physiologists.

It is scarcely to be wondered at that much confusion has arisen in medical circles. In one well-known work on neurology for instance, the sympathetic fibres to the bladder are depicted as leaving the spinal cord in the third, fourth, and fifth lumbar nerves, although in fact there are as a rule no white rami from these nerves. It would be easy to point out other errors of equal magnitude.

It is the purpose of the author to show that the autonomic nervous system in man is strikingly similar to that found in many animals, and that there is no need for a separate and dissimilar nomenclature. In this paper attention is confined largely to a consideration of the outflows to the lower abdominal and pelvic viscera. The sketch is incomplete, no attempt being made to review the literature exhaustively. The author endeavours rather to stress

outstanding facts which he has had an opportunity of verifying personally, and to present a clearly-defined picture which he hopes may be of service to medical men and to surgeons in particular.

PLAN OF THE AUTONOMIC NERVOUS SYSTEM.

It is assumed that the reader has a working knowledge of the plan of the autonomic nervous system as depicted by Gaskell and Langley. A description of the various outflows and arcs is beyond the scope of this paper.

NOMENCLATURE.

It is proposed to use largely the nomenclature employed by Langley. The nerve bundles passing forwards from the lumbar sympathetic trunks to the region of origin of the inferior mesenteric ganglion or ganglia will be called the 'inferior' or 'lumbar splanchnic nerves'. Certain bundles connecting the inferior mesenteric with the cœliac or superior mesenteric ganglion are named by Langley 'the ascending branch of the inferior mesenteric ganglion'. This appears to be an unsatisfactory title, as it is rather a root of the ganglion, and so it will be termed the 'cœliac root of the inferior mesenteric ganglion'. From the inferior mesenteric ganglion arise colonic branches, and the hypogastric nerves, right and left, which pass into the pelvis to take part in the formation of the pelvic plexuses. From certain sacral nerves arise the pelvic nerves which, after a short course, enter the pelvic plexus of the corresponding side. From the pelvic plexuses arise visceral branches to the rectum, bladder, and other pelvic organs. (*See Figs.* 407, 408, 410, 411.)

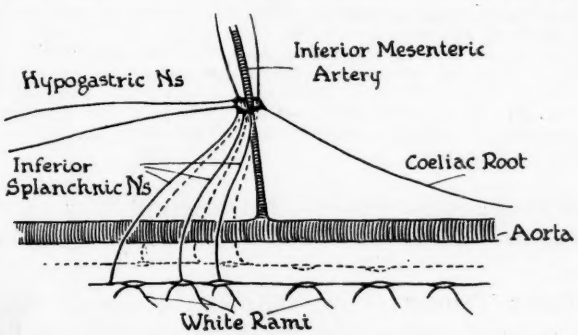

FIG. 407.—Diagrammatic representation of the lumbar outflow in the guinea-pig. The trunks lie close together. The lowest white rami enter the trunks well below the point of origin of the inferior mesenteric artery from the aorta. Similarly in relation to the artery the inferior splanchnic nerves arise low down and run ventrally and cranially on either side of the aorta to the inferior mesenteric ring, or ganglion, which is penetrated by the inferior mesenteric artery, as in other animals. The cœliac root enters the ganglion from above, and from the latter arise colonic branches and the hypogastric nerves. The trunks and inferior splanchnic nerves of the right side are represented by the interrupted lines. Actually the colonic branches are more numerous than shown in the diagram. Microscopically small ganglionic nodes are to be seen scattered in the 'ring'.

It is to be hoped that this nomenclature will displace the numerous terms found in anatomical text-books, such as 'aortic plexus', 'hypogastric plexus', 'nervus erigens', 'presacral nerve', 'intermesenteric plexus', and so on.

ANATOMY.

The macroscopic and microscopic anatomy of the autonomic nerves of the lumbar and sacral regions in rabbits, cats, and dogs was described in great detail by Langley and Anderson[1, 3] in a series of masterly papers. The author has made many dissections in dogs, cats, guinea-pigs, rabbits, opossums, monkeys, and human beings, and in all the general plan has been much the same, although minor variations are usually to be found.

The composition of the various nerve bundles has been studied by the method of teasing short segments in glycerin after immersion in a 1 per cent solution of osmic acid. In many instances nerves were divided in living animals and after the passage of six or seven days the animals were killed

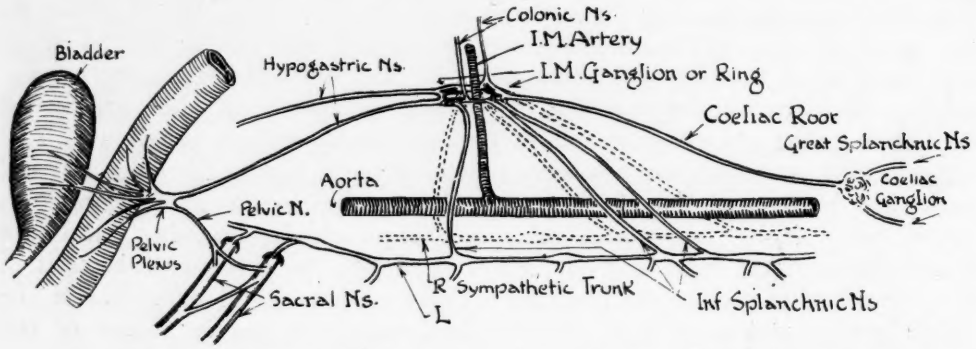

FIG. 408.—Diagram to show the arrangement of the lumbosacral nerves in the cat. The lumbar trunks lie close together. The inferior splanchnic nerves pass forward on either side of the aorta into the mesentery of the colon. In the region of the inferior mesenteric artery they unite to form stout bundles on either side united by decussating bands passing cranially and caudally to the artery so as to form a ring of nervous tissue encircling the vessel. The cœliac root passes into the ring, and from the latter arise numerous colonic branches and the hypogastric nerves. Several small ganglionic nodes are to be demonstrated in the 'ring', which, however, appears on superficial examination to be a large discrete nodule (*see Fig.* 414). The hypogastric nerves join up with the pelvic nerves to form the pelvic plexuses, which give branches to the pelvic viscera. The lesser splanchnic and renal nerves are not shown.

and degenerated fibres were traced. No attempt was made to count the fibres or to assess accurately the relative numbers of medullated and non-medullated fibres.

The Sympathetic Trunks (*Figs.* 408, 410, 411).—In the thoracic region each sympathetic trunk crosses the heads of the ribs and thus is situated quite close to the corresponding intercostal nerves. In the lower thoracic and lumbar regions the psoas muscle intervenes and the trunk passes forwards, skirting the medial border of the muscle and coming to lie on the antero-lateral aspect of the vertebral bodies a considerable distance from the lumbar nerves. Below the pelvic brim, the sacral trunk comes to lie close to the sacral nerves as they issue from the sacral foramina, and ends by joining with its fellow of the opposite side in the ganglion impar, situated low down in front of the coccyx. It should be noted that in small animals the two lumbo-sacral trunks are separated by a very small interval, whilst in man the interval is disproportionately greater. In the lumbar and sacral regions the trunks are connected by numerous fine twigs. Ganglia are found to correspond in

position more or less regularly with the vertebral bodies, but this is not an invariable arrangement. Fusion of two ganglia is frequently to be noted. The trunks between obvious ganglia contain both medullated and non-medullated fibres, the latter preponderating. The medullated fibres tend to remain near the surface and run in bundles (Müller[2]). Between the fibres are numerous scattered ganglion cells.

The Rami.—In the thoracic region the rami are quite short and the grey and white lie close together. In the lumbar area the grey rami pass almost directly backwards from the lateral chain to the appropriate spinal nerve accompanying the lumbar vessels under the arches of origin of the psoas muscle. They anchor the ganglionated trunks firmly so that the latter cannot be drawn ventrally until the grey rami are divided. Only a very short segment of a lumbar grey ramus is visible until the psoas muscle is removed (*Fig.* 409). The while rami take a long oblique course between the slips of

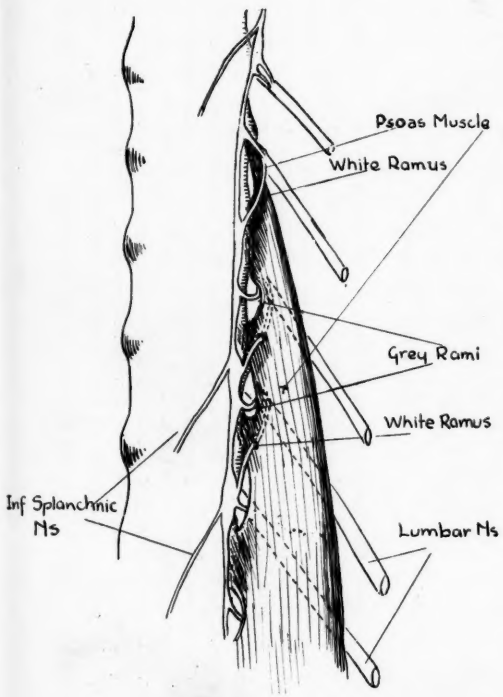

FIG. 409.—Diagram to show how the psoas muscle separates the lumbar sympathetic trunk from the spinal nerves. In the thorax, cranial to the highest slip of origin of the muscle, the trunk crosses the rib heads and lies quite close to the intercostal nerves, so that the rami are short and close together. In the lumbar region the trunk lies some distance from the lumbar nerves, so that the rami take a much longer course. The grey rami pass almost directly backwards, or backwards and downwards, from the trunk to the lumbar nerves in company with the lumbar vessels under the arches formed by the psoas muscle between the intervertebral discs. The white rami are obliquely placed, crossing the slips of origin of the psoas muscle and thus issuing from the surface of the muscle to join the trunks well below their point of origin. The grey rami always hug the vertebral bodies and never pierce the surface of the psoas muscle.

origin of the psoas muscle downwards, inwards, and forwards, to join the lumbar trunk well below their points of origin from the spinal nerves. They thus emerge from the ventral surface of the psoas muscle and are quite distinct from the grey rami. The white ramus from, say, the first lumbar nerve joins the trunk at or below the point of origin of the grey ramus in the second lumbar nerve (*Figs.* 409–411). The white rami are frequently duplicated and there may be more than two bundles (*Fig.* 410). In the dog the lowest white ramus springs from the third or fourth lumbar nerve, in Macaque monkeys usually from the third, though occasionally from the fourth, and in man from the second lumbar nerve. In the sacral region the grey rami are short and

pass obliquely outwards and downwards to join the sacral nerves. White rami do not arise from the nerves taking a major part in the formation of the limb plexuses.

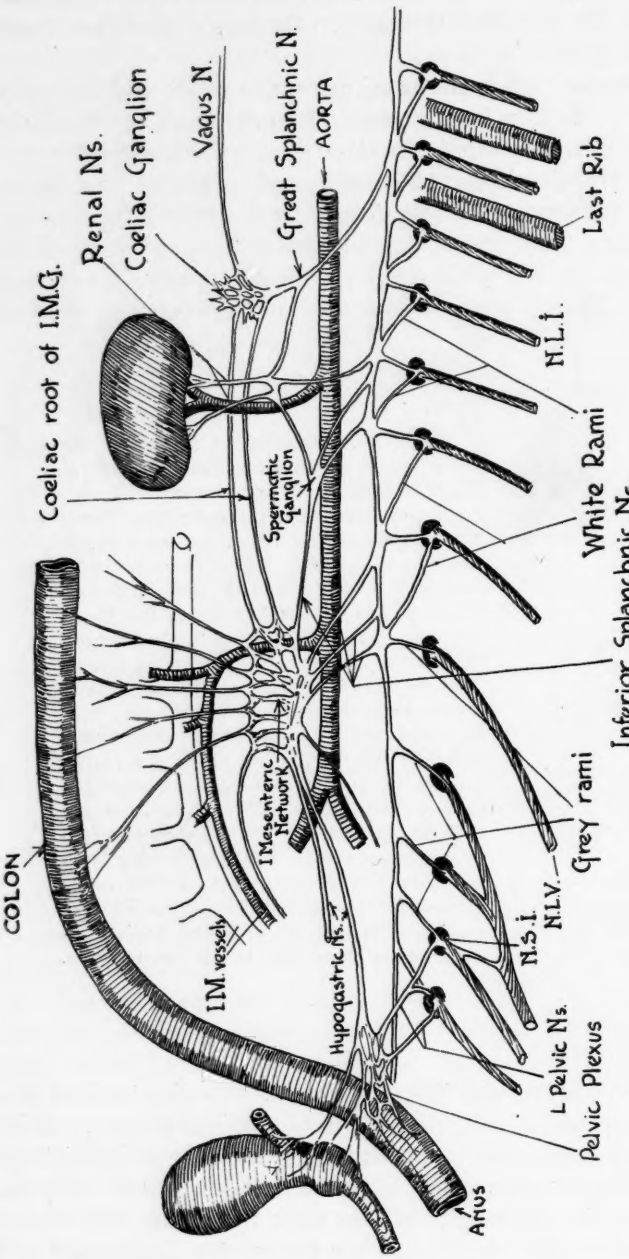

FIG. 410.—Diagram to show the arrangement of the lumbosacral autonomic nerves in Macaque monkeys, as seen from the left side, the kidney being shown ventrally. In the lumbar region the trunks are separated from the spinal nerves by the psoas muscle (not shown), so that the rami take a long course, the white passing obliquely between the slips of origin of the muscle and issuing from its ventral surface, the grey passing more directly and in company with the lumbar vessels under the arches formed by the muscle between its points of origin from the intervertebral discs. The coeliac roots join up with the uppermost inferior splanchnic nerves in a ganglionated network penetrated by the inferior mesenteric artery. From this network branches pass to join the thick paired ganglionated bundles formed by the union of the other inferior splanchnic nerves of each side. These bundles are connected by a stout decussating strand at their caudal extremities. Colonic branches spring from this network and bundles, and the hypogastric nerves arise from the caudal extremities of the lateral bundles. These nerves give branches to the ureters and pass on to the pelvis to take part in the formation of the pelvic plexuses. The left pelvic nerve is double in this case. The grey rami in the sacral region should have been drawn shorter, the trunks lying quite close to the sacral foramina. The inferior mesenteric ganglia are multiple and are found scattered in the network about the artery and in the paired lateral bundles below this level.

The white rami consist very largely of medullated fibres, which vary greatly in size. The grey rami are composed mainly of non-medullated fibres, but medullated fibres are commonly to be seen in fair numbers. The

proportion of medullated fibres appears to vary a good deal in different animals, but the author has not examined sufficient material to be worthy of record. Langley[4] discusses the question of origin and destination of the medullated fibres found in grey rami. They may be preganglionic fibres which have not made connection with cells in the ganglia of the lateral chains, but are passing to do so with cells situated further afield. They may be medullated postganglionic fibres, while some may be afferent fibres passing from the periphery via the grey rami to the trunks and so via the white rami to the appropriate posterior root ganglion.

The Lesser Splanchnic Nerves (*Figs.* 410, 411).—Below the lowest root of the great splanchnic nerve, arising from the thoracic and the upper lumbar trunks, are a varying number of branches which pass to the region of origin of the renal vessels. These freely anastomose and give off branches to the kidneys and adrenal glands, some to the cœliac ganglion, and often one or more branches to the region of the inferior mesenteric ganglion or network and the spermatic or ovarian ganglion. These nerves are composed mainly of medullated fibres. Whilst they are described as branches arising from the trunks, probably the great majority of the fibres arise from cells in the spinal cord and merely pass through the trunks without making contact with ganglion cells situated therein.

The Inferior or Lumbar Splanchnic Nerves (*Figs.* 407, 408, 410, 411).—This name should be reserved for nerves passing to the inferior mesenteric ganglion and should not include the lesser splanchnic nerves arising from the upper lumbar trunks. They arise from the upper lumbar trunks and pass medially downwards and forwards round the aorta to reach the inferior mesenteric ganglion. On the right side they usually pass between the inferior vena cava and the aorta. They are variable in number (from two to four on each side) and point of origin, most commonly arising opposite the first, second, and third lumbar vertebræ. In man the more cranially situated of these nerves pass more directly forwards round the aorta and then turn sharply downwards in company with the cœliac roots of the inferior mesenteric ganglion, often communicating with the spermatic or ovarian ganglion (*Fig.* 411). Hence, they have been described in anatomical text-books as branches 'reinforcing' the 'aortic plexus'.

The lesser splanchnic nerves and the inferior splanchnic nerves are composed in the main of medullated fibres of varying size. The fibres degenerate on the distal side of a point of section, or after section of the white rami, showing that the cell bodies are situated centrally.

The Cœliac Root of the Inferior Mesenteric Ganglion (*Figs.* 407, 408, 410, 411).—This is constantly present and is usually represented by two or more nerve bundles springing from the cœliac or superior mesenteric ganglion or from nerves in the vicinity. Frequently the lesser splanchnic nerves or renal nerves may add a contribution. The bundles pass downwards in front of the aorta, usually communicating with the spermatic ganglia, to join up with the inferior splanchnic nerves at the inferior mesenteric ganglion. Nerve fibres of the cœliac root are mainly non-medullated, but medullated fibres are present in fair numbers. In dogs these degenerate on the caudal side of a point of section through the root at any point or after section of the great

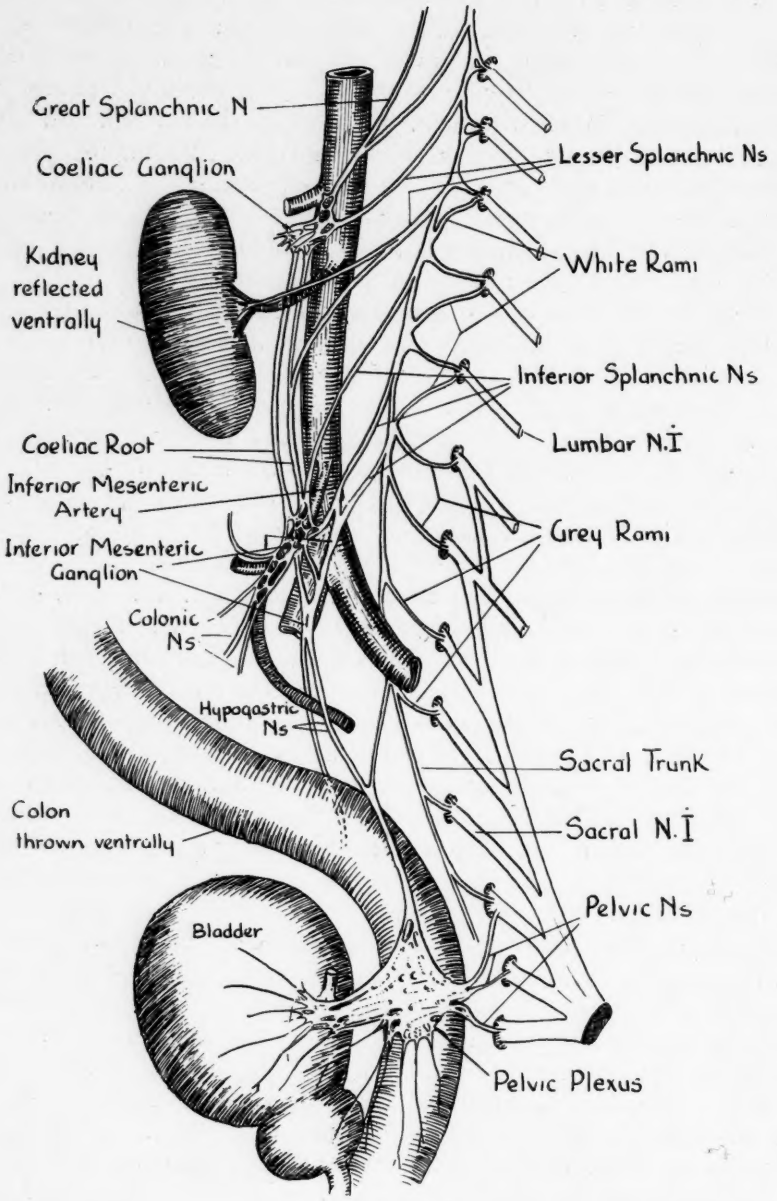

FIG. 411.—Diagram to show the arrangement of the lumbar and sacral autonomic nerves in man. The kidney and colon are thrown ventrally. The rami are much the same as in animals, and have the same relationship to the psoas muscle (not shown, *see Fig.* 409). The inferior splanchnic nerves and the cœliac root of the inferior mesenteric ganglion are clearly to be seen. The inferior mesenteric ganglion is similar to that shown in *Fig.* 412. The hypogastric nerves pass downwards into the pelvic plexuses. On the left side the hypogastric nerve receives a twig from the trunk. The pelvic nerve is represented by twigs from the second, third, and fourth sacral nerves. From the widespread ganglionated pelvic plexus numerous visceral nerves pass to the bladder, prostate, rectum, etc.

splanchnic nerves. Thus the nerve cells are probably situated in the thoracic portion of the spinal cord or in the posterior root ganglia.

The cœliac root of the inferior mesenteric ganglion and the inferior splanchnic nerves have been described by Learmonth[5] in recently published papers as the roots of the 'presacral' nerve. This author deplores the "too slavish a transference of the arrangement in animals to conceptions of human physiology". The present author is definitely of the opinion that there is a very close resemblance between the systems found in animals and man. Learmonth's terminology serves only to obscure the plan in man, and his description of the inferior splanchnic nerves and the inferior mesenteric network is distinctly misleading.

The Inferior Mesenteric Ganglion or Ganglia.—Langley and Anderson[1] point out that in the cat the ganglion consists of several distinct nodes, and they mention that Navrocki and Scabitchewsky (1891) had previously noted this fact. Many present-day authors appear to have overlooked this work.

In dogs, guinea-pigs, cats, and rabbits (*Figs.* 407, 408, 413) the ganglion is represented by several nodules in close proximity, connected by nerve bundles so as to form a ring of nervous tissue encircling the inferior mesenteric artery. The ring is usually made up as follows: Two or more of the inferior splanchnic nerves on each side fuse in a small ganglionic node which receives also twigs from the cœliac root. A nerve bundle passing transversely cranial to the inferior mesenteric artery connects the two nodes, which may appear to be fused into a single mass, and fasciculi pass caudally from them on either side of the artery to enter small ganglia, which also receive the more caudally situated inferior splanchnic nerves. The lateral bundles are longer in rabbits than in cats and dogs (Langley and Anderson[1]). The distal ganglia are connected by a short transverse nerve placed caudal to the artery, and give origin to the hypogastric nerves. From the ring of nerve tissue arise numerous nerves which run in company with the branches of the artery to the colon.

In Macaque monkeys (*Fig.* 410) the arrangement is very similar, but somewhat more complex. The cœliac roots and the uppermost inferior splanchnic nerves of each side, which usually communicate with the spermatic or ovarian ganglion, enter a ganglionated network which is penetrated by the inferior mesenteric artery. From this plexus numerous colonic nerves arise, the uppermost of which may be traced to the region of the superior mesenteric plexus with which they appear to communicate, and also bundles passing caudally on each side of the artery, which are joined by the remaining inferior splanchnic nerves. Thus augmented, the thick lateral bundles run parallel for about 2 cm. At their caudal extremities they are firmly connected by a short stout transverse strand, and from this point the two hypogastric nerves arise and diverge. From the ventral aspect of the lateral bundles a large number of colonic nerves arise, which pass in the mesentery to the colon. Ganglionic nodes are to be found in the network which surrounds the artery and in the lateral bundles.

As the whole of the network lies between the peritoneal layers of the mesocolon, it is flattened in a sagittal plane and the lateral bundles at first sight appear to be one thick bundle (*Fig.* 410).

In man the arrangement is again very similar (*Figs.* 411, 412). The cœliac root, represented by several small nerves as a rule, passes into a network of nervous tissue which is penetrated by the inferior mesenteric artery. Into this network pass also stout contributions from the more cranially situated of the inferior splanchnic nerves. The latter give origin in addition to fasciculi which join up with the more caudally situated inferior splanchnic nerves to form thick ganglionated nerve bundles on either side of the mid-line. These

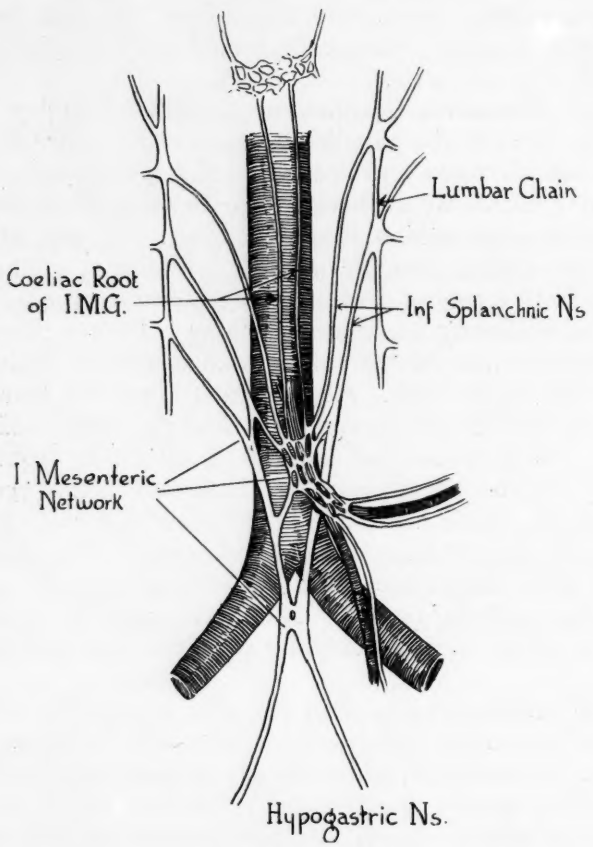

FIG. 412.—Diagram to show the formation and disposition of the inferior mesenteric network or ring in man, which corresponds to the 'ganglion' of animals. The 'ring' is formed above by the meeting of the cœliac root and the inferior splanchnic nerves, and ends below at the point of divergence of the hypogastric nerves. The inferior mesenteric artery penetrates the ring. Ganglia are invariably to be found scattered throughout the network, fairly large nodes being present as a rule in the thick lateral bundles formed by the fusion of the inferior splanchnic nerves.

bundles converge and meet at a point usually some little distance below the bifurcation of the aorta, but occasionally higher up in the region of the proximal part of the inferior mesenteric artery. At the point of meeting of the bundles there appears to be a free decussation of fibres, and from this point also arise the hypogastric nerves, right and left. Small connecting twigs commonly pass between the various parts of the network just described.

Ganglionic nodes are to be found commonly in the bundles formed by the union of the inferior splanchnic nerves on each side, scattered throughout the network surrounding the inferior mesenteric artery, and at the point of union of the bundles at the lower end of the network. Seldom do the nodes reach very large proportions, but almost invariably there is a considerable amount of ganglionic tissue present, distributed as outlined above. Occasionally the network is compressed and then larger ganglia are to be seen.

For the reasons just stated it is difficult to define the inferior mesenteric ganglion in man.

The whole of the network, extending from the points of union of the inferior splanchnic nerves on each side down to the point of emergence of the hypogastric nerves, and including the ganglionated network on the inferior mesenteric artery above described, is to be looked upon as representing in man the ganglionated ring seen in animals and known as the inferior mesenteric ganglion or ganglia. It has been pointed out that even in small animals where this appears to be a solitary node, it is not so in fact. In animals the descending colon is provided with a free mesentery and the sympathetic trunks lie close together, so that the inferior splanchnic nerves of each side run towards the inferior mesenteric ganglion in close proximity. In addition the inferior mesenteric artery leaves the aorta almost at a right angle. Thus it comes about that the inferior mesenteric ganglionated network is compressed and appears at first glance to be a discrete ganglion. In man the trunks are widely separated, the inferior splanchnic nerves converging sharply towards the mid-line. There is no free mesentery and the inferior mesenteric artery lies practically on the ventral wall of the aorta, which effectively prevents any compression of the inferior mesenteric ganglionated network. These factors probably explain why the network spreads laterally so much more in man than in animals.

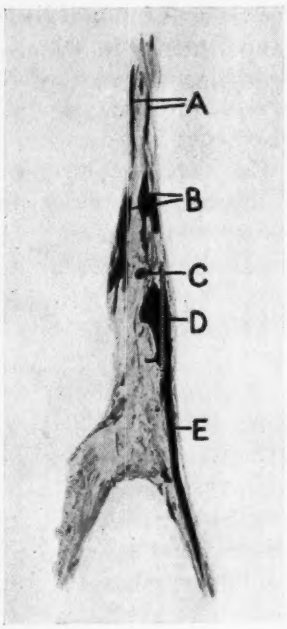

FIG. 413.—Photograph of a coronal section through the inferior mesenteric ganglion of a cat. The various nerves were stretched out before embedding in paraffin in order to ensure that they would lie in the same plane. Above, the inferior splanchnic nerves (A) and the cœliac root enter the 'ring'. Paired proximal ganglia (B) are plainly seen. Lateral bundles pass from these on either side of the inferior mesenteric artery (C) into ganglia (D) situated caudal to the vessel. One of these is not seen in the section. An indication of the transverse bundle connecting the two distal ganglia is seen. The hypogastric nerves (E) diverge below. (×3.)

A study of several microscopic sections of a fœtus (about four months) showed clearly the multiple nature and bilateral arrangement of the ganglia in the region of the inferior mesenteric artery, although in this case they were situated close together as in small animals (*Fig.* 414).

Learmonth[5] remarks that in man there is no ganglion corresponding to the inferior mesenteric ganglion of animals, or that it is small and of little importance. He ignores the fact that in animals the ganglion is in the nature

of a ganglionated network, and that the same network in man contains a considerable amount of ganglionic tissue. Coates[6] refers to 'rudimentary ganglia'. Why it should be assumed that the ganglia are rudimentary (Coates) or of little importance (Learmonth) is not clear. Leriche and Fontaine[7] pointed out that there are scattered cells and microscopic ganglia in the 'presacral nerve' amongst others. They consider that their 'discovery' of these is enough to invalidate certain conclusions arrived at by Langley after experiments in which nicotine was applied locally to the inferior mesenteric ganglia. It was, of course, well known to Langley that many of the fibres

FIG. 414.—Photomicrograph of a horizontal section through the region of the inferior mesenteric ganglion in a fœtus (about four months). Ventral to the aorta is seen the inferior mesenteric artery surrounded by ganglia and nerves. Serial sections showed distinctly the bilateral nature of this 'ring' and the multiplicity of ganglia. (×46.)

of the inferior splanchnic nerves pass by the inferior mesenteric ganglion to relay at cell stations further afield, and he did not neglect this fact in arriving at his conclusions.

The Hypogastric Nerves.—In animals these are represented by two or more nerves which arise from the inferior mesenteric ganglion and, diverging, pass downwards, not in company with the inferior mesenteric artery, to take part in the formation of the pelvic plexuses. There are frequently small communicating strands uniting the hypogastric nerves with the lumbosacral sympathetic trunks, which are to be looked upon as subsidiary inferior splanchnic nerves. In man the arrangement is much the same. The inferior mesenteric ganglionated network divides below into two complex fasciculated bundles, one passing on either side of the rectum to enter the corresponding pelvic plexus. The hypogastric nerve bundles contain scattered nerve cells

and sometimes small ganglionic nodes. These are to be regarded as outlying parts of the inferior mesenteric ganglion. As in animals, the hypogastric nerves frequently receive reinforcing twigs from the lumbar or sacral trunks, which may pass posterior to the external iliac arteries. They give several branches at different levels to the ureter of the corresponding side. The hypogastric nerves are composed of large numbers of non-medullated and many medullated fibres. The majority of the medullated fibres degenerate after section of the inferior splanchnic nerves, hence the nerve cells are situated in the lumbar segments of the spinal cord. The fibres decussate in part in the inferior mesenteric ganglion, so that each hypogastric nerve receives fibres from the inferior splanchnic nerves of each side of the body (Langley and Anderson[8]). Langley and Anderson[1] point out that after degenerative section of one pelvic nerve some of the fibres of the corresponding hypogastric nerve degenerate. In the cat these are very few, in the rabbit they are more numerous. The author has noted that in monkeys a few fibres of the hypogastric nerve degenerate after section of the pelvic nerve of the same side. The destination of these fibres has not yet been traced. No similar observations in man are as yet to hand.

The Pelvic Nerves (*Figs* 408, 410, 411).—Fine twigs, arising from two or more of the sacral nerves just after they issue from the sacral foramina, unite to form the pelvic nerves, one on either side of the body. Occasionally the nerve may be represented by two bundles. In dogs, cats, and monkeys the pelvic nerve is usually single, discrete, and about an inch or more in length. It passes distally into the pelvic plexus. In man the nerve twigs pass almost at once into the pelvic plexus, so that, as a rule, no definite single nerve may be demonstrated. The pelvic nerves are composed almost entirely of medullated fibres of varying size.

The nerves arise as a rule from two or more of the sacral nerves, but tend to vary somewhat, as do other plexuses, in actual level. Thus in the cat the main outflow is from the second sacral nerve, with variable contributions from the first and third (Langley). In the dog the second and third sacral nerves supply the main contributions. In Macaque monkeys the pelvic nerves arise from the first and second sacral nerves, in man from the third and either the second or the fourth, or both.

The Pelvic Plexus (*Figs.* 408, 410, 411).—This is a network composed of interlacing twigs resulting from the breaking up of the hypogastric and pelvic nerves. In it are situated numerous small ganglionic nodes. The network spreads out in a fan-shape from the points of entry of the above-named nerves, which are fairly close together. From the plexus many fine twigs radiate to the different organs in the pelvis, most of which are mixed nerves containing fibres from both of the parent nerves or from the ganglia of the plexus. In man the network is well developed and its branches are very numerous. Ganglionic nodes are more numerous near the point of entry of the hypogastric nerve. The visceral branches of the pelvic plexuses are composed of non-medullated and medullated nerve fibres. The former probably belong mainly to the lumbar sympathetic outflow, and have their cells situated either in the ganglia of the inferior mesenteric network or the pelvic plexus. The latter belong almost entirely to the sacral outflow, as they degenerate after

section of the pelvic nerves (dogs and monkeys). The cell stations for this group of fibres are situated on or in the walls of the viscera in question, at least in part.

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MALIGNANT ADENOMA OF THE PROSTATE WITH SECONDARY GROWTHS IN THE VERTEBRAL COLUMN SIMULATING POTT'S DISEASE.

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This case is described for two reasons. In the first place, the clinical and pathological findings in the central nervous system were of such interest as to deserve being placed on record. Secondly, the case was a good example of the well-recognized but often extremely confusing picture that results from the remote metastases of a hidden primary focus of malignant disease. In such a case as the present one, the youth of the patient adds to the diagnostic difficulties by tending to divert suspicion from the possibility of such a hidden primary focus and also from its particular site—in this instance the prostate gland.

History.—The patient was a man aged 30, a printer, who was well until four months before admission to the West End Hospital for Nervous Diseases. His first symptoms were pain and stiffness low down in his back, appearing insidiously, and the condition had been diagnosed as "muscular rheumatism". The symptoms grew gradually more severe, and the next development was that the patient felt as though he were "walking on rubber", and weakness of all four limbs slowly appeared and progressed. Three weeks before admission the patient was quite unable to stand and found it difficult to pass urine. Numbness had spread to the abdominal wall. From this time onwards the condition progressed rapidly until spastic paraplegia with distension-overflow from the bladder and retention of fæces were marked, with complete anæsthesia of trunk and legs below the nipple line and with great weakness of the hands. The intrinsic muscles of both hands showed wasting and other signs of lower motor neuron atrophy. An ascending urinary infection had developed, the urine being alkaline and containing much pus and albumin and enormous numbers of mixed organisms, e.g., streptococci and staphylococci, gram-negative and gram-positive bacilli; *Bacillus proteus* predominated in the cultures.

On Examination.—A marked chronic pustular acneiform eruption was present over the back, and the pustules contained *B. proteus*—presumably secondary to the bladder infection—in addition to *Staphylococcus albus*. An examination of the cerebrospinal fluid obtained by lumbar puncture showed a definite Froin's syndrome—xanthochromia and fibrin clot on standing—with approximately 1 per cent of total protein and an extremely marked

excess of globulin. Cell-count: 5 small lymphocyte-like cells per c.mm. in the first fraction drawn off; in the second, 3 cells per c.mm. Wassermann and Kahn reactions negative (these being also negative in the blood). Lange's colloidal gold curve 0001223332.

A cisternal injection of lipiodol was given and the patient was X-rayed, cerebrospinal fluid from the cistern being examined. The normal findings in this may be compared with those of the lumbar puncture fluid described above. It was clear and colourless. Cell-count: 2 small lymphocyte-like cells per c.mm. Total protein: 0·02 per cent. Globulin: no excess. Wassermann and Kahn reactions negative, and Lange curve 0011000000.

A blood-count showed some degree of polymorphonuclear leucocytosis: total leucocytes 15,200 per c.mm., polymorphs 80 per cent.

The X-ray findings are described below. A diagnosis of a spinal tumour in the lower cervical region was made. Death occurred suddenly following an attack of vomiting and before laminectomy could be carried out.

Pathological Examination.—Those parts of this examination which are relevant are described. The body was that of a well developed young adult male with a profuse pustular eruption over the back.

Removal of Spinal Cord.—On beginning this removal the spinous processes of the 7th cervical and 1st dorsal vertebræ were seen to be unusually prominent and they were distinctly movable. The laminæ of these vertebræ, on sawing them through to open up the spinal canal, were found to be pathologically softened. When the spinal cord had been exposed the lower part of the cervical enlargement was found to be markedly softened also. The bodies of the 7th cervical and 1st dorsal vertebræ showed an abnormal degree of projection backwards, so that they had pressed on the cord, causing the softening and tending to occlude the spinal cord.

The spine at the level of the bodies of the two affected vertebræ was unduly movable, producing the general appearance of a fracture-dislocation supervening upon disease of the bone such as neoplasm or tuberculosis. The head and neck of the first rib on the right side also showed extensive softening.

A portion of the spinal column from the 6th cervical to the 3rd dorsal vertebra inclusive was removed with the proximal parts of the ribs attached, so as to include all the diseased area. An X-ray photograph was taken of it (*Fig.* 415), and the specimen was then divided sagittally (*Fig.* 416). The bodies of the 7th cervical and the 1st dorsal vertebræ are seen to be almost entirely destroyed by disease, and collapse has taken place, so that the corresponding intervertebral discs are practically touching one another. The middle one of these three discs has been displaced backwards, and, as shown in the illustration, has been the chief agent in compressing the spinal cord. The body of the 2nd dorsal vertebra shows considerable softening posteriorly, but remains uncollapsed.

The disease process had also spread laterally so that the transverse processes of the 7th cervical and 1st and 2nd dorsal vertebræ were invaded and softened, the right side being most affected. The articular surfaces of the 1st and 2nd ribs on the right side were involved and the head of the former partially destroyed. The lateral attachments of the 1st dorsal neural arch

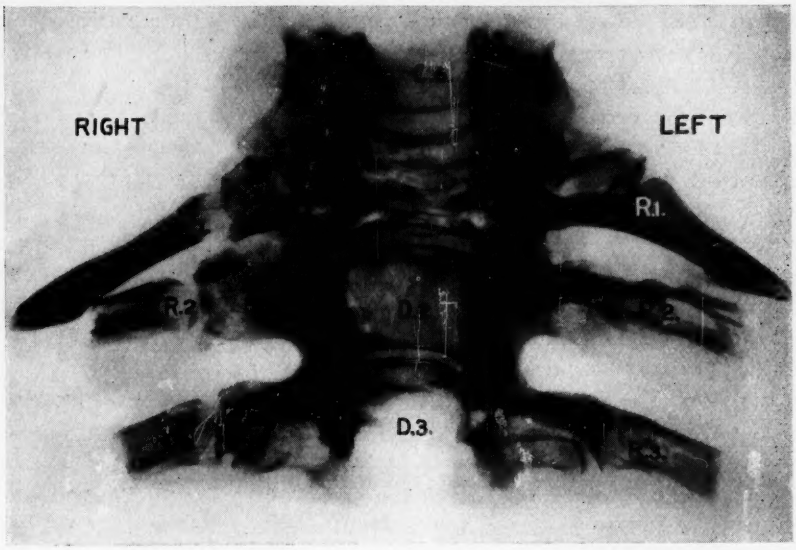

FIG. 415.—Radiogram of specimen after removal. It includes from the 6th cervical to the 3rd dorsal vertebræ, with the proximal portions of the upper three pairs of ribs. The neural arches have been cut away for the removal of the cord. The bodies of the 7th cervical and 1st dorsal vertebræ have collapsed, and the three intervertebral discs above, between, and below have been crushed together and are almost touching one another. There is also some rarefaction of the body of the 2nd dorsal vertebra, and of the transverse processes of the 1st and 2nd dorsal vertebræ on the right side, as well as of the heads and necks of the 1st and 2nd right ribs.

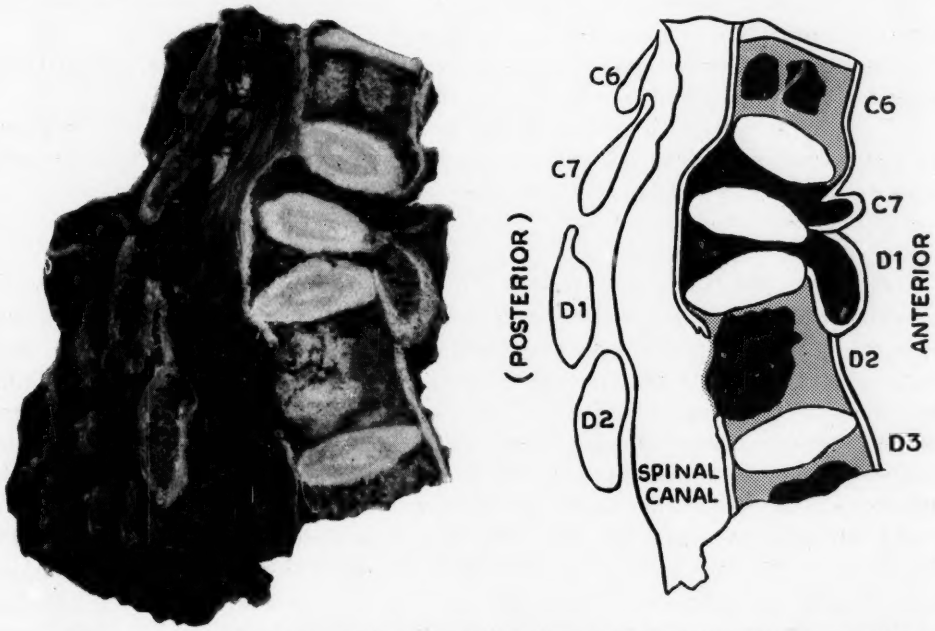

FIG. 416.—Mesial vertical section through specimen after removal, the corresponding radiogram of which is shown in *Fig.* 415. The collapsed condition of the bodies of the 7th cervical and 1st dorsal vertebræ is shown, and also the extensive malignant growth in the still uncollapsed body of the 2nd dorsal and slighter involvement of the 6th cervical and 3rd dorsal. The backward thrust of the three intervertebral discs, especially the middle one, into the spinal canal, by which the cord was compressed, is also shown. The areas invaded by the tumour are shaded in black in the key sketch. ($\times \frac{3}{4}$).

were affected, this leading to the movability of the spinous process as noted. The 1st dorsal nerve-roots on both sides were involved in the foramina and seemed totally destroyed.

The tissue in the softened areas of bone was of a pale yellowish-white colour, granular and crumbling. Much pseudocystic cavitation was present. The impression was gained that this tissue consisted of a metastatic deposit of a malignant tumour, and was not tuberculous.

Spinal Cord.—No evidence of neoplastic involvement of the cord itself was found. Naked-eye and microscopical sections of the compressed area showed generalized non-inflammatory degeneration, the white matter being fenestrated and spongy and the ganglion cells of the grey matter all showing advanced necrotic changes.

Thorax.—Well-marked hypostatic bronchopneumonia was present in both lungs, and the myocardium showed cloudy swelling and fatty changes.

The bronchial lymph-glands at the roots of the lungs were slightly enlarged, especially on the left side. They were, in parts, unusually pale and granular, and were removed for section, as were also some enlarged lateral inferior deep cervical (supraclavicular) glands.

Prostate.—This was only very slightly enlarged, but on section there was some slight suggestion of nodulation of the cut surface. Recent thrombosis of the veins of the prostatic plexus was present; and there was some enlargement of the neighbouring pelvic lymphatic glands, as well as of a few of the retroperitoneal glands along the course of the abdominal aorta.

Microscopical Examination.—Sections of the prostate showed the presence of an adenoma which had become malignant (*Figs.* 417, 418).

The enlarged lymphatic glands examined—pelvic, bronchial, and cervical—showed infiltration with the same malignant growth.

Figs. 419 and 420 show a low- and a high-power view of the tissue in the softened areas of the spinal column and reveal the presence of a metastasis of the same tumour. Very little bone is left.

SUMMARY.

A case of primary prostatic adenocarcinoma in a man of 30 is described. Metastases in the pelvic, prevertebral abdominal and thoracic, and deep cervical lymph-glands and in the bone of the vertebral column were found, the latter involving the bodies of especially the 7th cervical and 1st dorsal vertebræ and adjacent portions of the spinal column and ribs, producing collapse of the vertebral bodies and a condition simulating Pott's "angular curvature", with compression and softening of the spinal cord, Froin's syndrome with xanthochromia, etc., and the sudden death of the patient. The difficulties of diagnosis are explained and the clinical course and pathological findings are outlined. The changes in the spinal column were an indication of the tendency of a prostatic neoplasm to metastasize in bone, and were localized to the region described.

The case therefore differs from the unusual case described by Roberts,[1] where there was a continuous direct spread of the growth on the intraspinal surface of the dorsal wall of the spinal canal from the sacral to the cervical

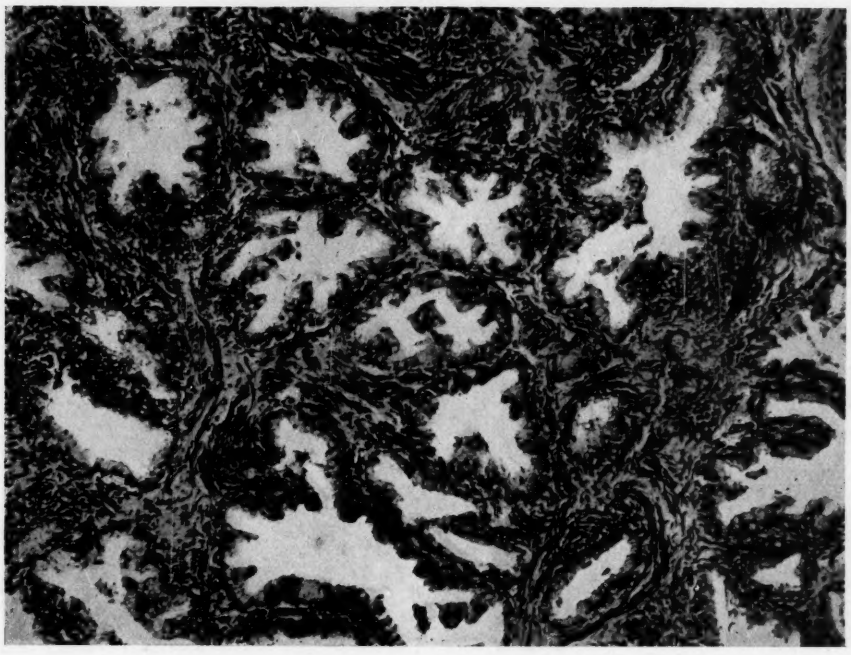

FIG. 417.—Low-power of the prostatic adenoma showing commencing malignancy. In other parts it has the appearance of a ' simple ' adenoma. In this portion it is commencing to show increased complexity, and in other areas there is distinct malignant metaplasia of the epithelial cells and infiltration of the stroma. Compare with *Fig.* 418. (Van Gieson and hæmatoxylin.) (× 100.)

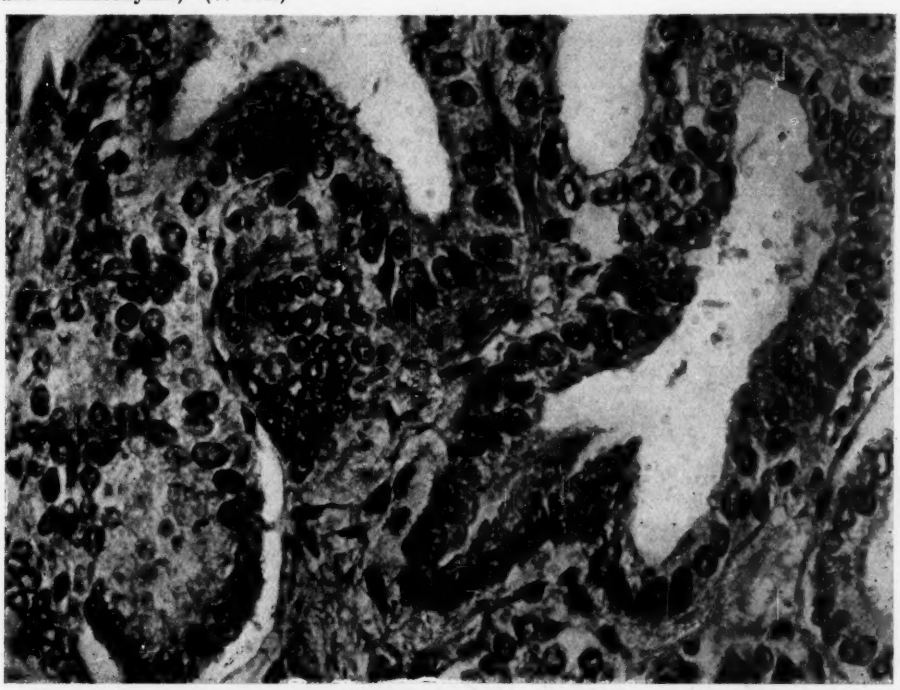

FIG. 418.—High-power of a portion of the prostatic tumour showing metaplasia to malignant adenoma or adenocarcinoma. There is active nuclear proliferation, and in some parts the cells form plasmodial masses, with imperfect division of their cell-bodies. (Van Gieson and hæmatoxylin.) (× 400.)

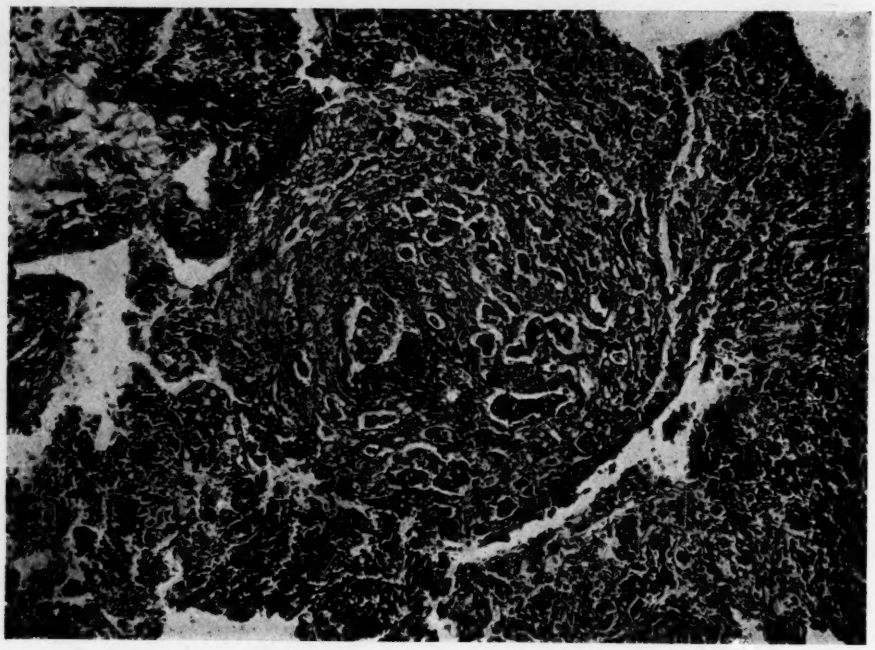

FIG. 419.—Low-power section of the tumour invading the body of the 1st dorsal vertebra. The tissue was cut without decalcification and is rather thick. It contained only a few small spicules of bone in process of absorption, and there was no irritative bony proliferation. (Hæmatoxylin and eosin.) (× 100.)

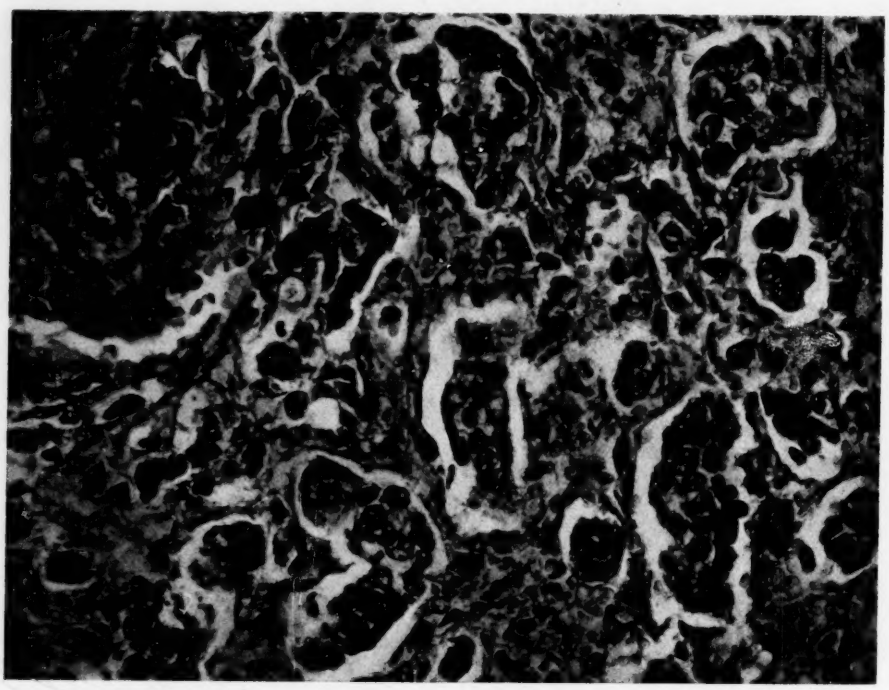

FIG. 420.—High-power of section seen in *Fig.* 419. A small fragment of partially absorbed bone is seen at the upper left corner. Numerous groups of the invading malignant glandular cells are shown. (Hæmatoxylin and eosin.) (× 400.)

region, though his theory that there is an intraspinous pathway for the dissemination of prostatic carcinomata consisting of the spinal laminæ with their ligaments and the lymph-spaces connected with these structures, might be considered in this case. It may also be mentioned that in the present case the bony metastases were completely osteoclastic and showed no evidence of the osteoplastic process which is generally described as characteristic of prostatic skeletal metastases.

We are indebted to Dr. E. D. Macnamara for the clinical notes of this case, which was under his care; to Dr. Martin Berry and his assistant Mr. A. York for the radiogram; and to Mr. J. Ottewill for his skilled technical assistance.

REFERENCE.

[1] ROBERTS, *Brit. Jour. Surg.*, 1928, xv, 652.

PRIMARY CARCINOMA OF THE LIVER:

WITH REPORT OF CASE SUCCESSFULLY TREATED BY PARTIAL HEPATECTOMY.

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Carcinoma occurs only very rarely as a primary disease of the liver, in marked contrast to secondary growths, which are extremely common in this organ. Up to sixty years ago observers believed the reverse to be the case, and, in spite of Virchow's warning in regard to the importance of searching for a primary focus with meticulous care, many cases were reported which were later discredited.

HISTORICAL SURVEY.

Kelsch and Kiener[28] in 1876, in reporting two cases of primary carcinoma of the liver, were able to find only one other authentic case in the literature. Accurate knowledge of the subject really begins in 1884 with the work of Sabourin,[37] who added a series of four cases. Four years later Hanot and Gilbert[21] presented a comprehensive contribution which marked a distinct epoch in the study of the disease. They described three gross types: (1) Nodular, (2) Massive, and (3) Cancer with cirrhosis; and recognized two varieties microscopically: (1) Alveolar; and (2) Trabecular. This remained the standard work for many years.

In 1901 Eggel[13] collected 163 cases (of which only 117 had been studied microscopically) and added one of his own. He abandoned the idea of a separate cirrhotic type, because he believed that cirrhosis in some degree was present in all cases, and adopted the following classification from the point of view of gross morbid anatomy: (1) Nodular—where the liver contains several tumour nodules, varying in size, and generally well circumscribed; (2) Massive—where the tumour consists of one large mass, occasionally associated with metastases; (3) Diffuse—where the tumour process appears to extend throughout the whole liver substance.

Wegelin[46] in 1905 described 8 cases, but the next advance of note was made by Yamagiwa[52] in 1911. He disagreed with the French writers in regard to the impracticability of their fine histological differentiation and made two simple divisions: (1) Hepatoma, i.e., carcinoma of hepatic cells; and (2) Cholangioma, i.e., carcinoma of bile-ducts. The term 'hepatoma' had previously been used by Sabourin in reference to a condition of nodular hyperplasia which in his opinion was a transitional stage between adenoma and carcinoma. Most modern writers, however, accept Yamagiwa's interpretation, and use it as a term for primary carcinoma of the liver cells. By 'cholangioma' is meant "only those carcinomata arising from the smallest bile canaliculi, and not those from other parts of the biliary apparatus".

Although later research work and literature have been voluminous, the broad views of Eggel, as modified by Yamagiwa, are now almost universally accepted as being the most satisfactory.

INCIDENCE.

There is no dearth of cases in the literature, and it is reasonable to assume that this is largely due to the general interest attached to a disease of such rarity. For this reason it is also probable that the majority of cases occurring during this century have been reported.

As secondary growths of the liver are so common and it is extremely difficult in all cases absolutely to exclude the possibility of a primary focus—such as, for instance, a small nodule in the kidney or adrenal—there is bound to be considerable overlapping in the available statistics from all sources. This would account to some extent for the wide variation that occurs in the reports of various observers. Added to this, there is no doubt that the incidence of the disease varies greatly in widely separated geographical areas.

An analysis of all available reports shows that the average incidence varies from 0·1 to 0·3 per cent of all autopsies in Europe and North America.

INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER.

Winternitz[48]	Analysis to 1916 Johns Hopkins Hospital	0·028–0·3 per cent 3 in 3700 cases =0·08 per cent
Wheeler[47]	Guy's Hospital to 1909	6 in 5000 cases = 0·1 per cent
Counseller and McIndoe[10]	Analysis, Eggel to Mayo, 1926	62 in 42,276 cases = 0·08 per cent
Brines[6]	Analysis, 1933	Average, 0·8 per cent
Clawson and Cabot[9] ..	University of Minnesota, 1923	1 in 5100 cases = 0·002 per cent
Fried[16]	Harvard, 1924	Only 1 reported case

Geographical Variations.—L. W. Smith[40] in 1926 found 12 out of 877 consecutive necropsies, i.e., 1·3 per cent, during one year in the Philippine Islands. Less than 70 of these deaths were due to malignancy, so that 17 per cent of all deaths associated with malignant disease were due to primary carcinoma of the liver. He mentions that "incidentally it is of passing interest to state that during the interval fully as many patients went home from the Philippine General Hospital with the clinical diagnosis of malignant disease of the liver as came to necropsy, and there seems to be no reason to doubt the clinical diagnosis as all the cases coming to necropsy were recognized ante-mortem."

Strong and Pitts[41] reviewed 9 cases collected at the Vancouver General Hospital (1920–7) out of a series of 1024 autopsies, giving an incidence of

0·87 per cent. Eight of these patients were Chinese, so that the percentage out of 115 autopsies on Chinese was 6·9 per cent. In the 909 autopsies on white patients primary carcinoma of the liver was found only once, i.e., 0·11 per cent, which agrees with the foregoing figures for white races.

Pirie[34] in 1921, writing at the South African Institute for Medical Research, concluded that carcinoma, generally speaking, is not so common in Africans as amongst Europeans, but in his experience primary carcinoma of the liver appears to be relatively more common.

If the figures are excluded for those where there is an abnormally high occurrence of the disease—due presumably to some local factor—the incidence does not exceed 0·3 per cent of all autopsies.

However, Brines[6] recently gave a detailed report on 8 cases of primary carcinoma of the liver out of 1087 necropsies at Detroit Receiving Hospital (1929–32). This, with 3 additional cases referred to in brief, gives an autopsy incidence of 0·8 per cent, which is considerably higher than that usually recorded.

According to Jaffe,[25] primary carcinoma of the liver occurs in 1·5 to 3 per cent of all cancers.

Age Incidence.—Eggel, in his original survey, gave the average age incidence for men as 53·1 years, for women 52·2 years. Ewing[14] stated that the disease occurs mainly between 40 and 60 years, especially between 50 and 60, while biliary carcinoma is relatively late, rarely occurring before the age of 40 years. However, a survey of the literature shows that no age is exempt. One patient in the Strong-Pitts series was 76 years old (average 45·6 years), while Müller[32] recently reported a case in a patient who was 83 years of age.

At the other extreme of age, in the experience of numerous observers (Allbutt[1], Castle[8], Dansie[11], Griffith[19], Wollstein[49]) the disease has been found in children of all ages and even in infants from the moment of birth. The occurrence of such early cases raises the possibility of some of these tumours being of an embryonal nature, and some at least of them have been described as such. It is agreed by these workers that though primary carcinoma of the liver does occur in infancy and childhood it is definitely rarer than in adult life, while the occurrence of sarcoma is of even greater rarity than carcinoma.

Sex Incidence.—Eggel's sex incidence figures were 63·3 per cent in men, 36·7 per cent in women; according to Karsner[26] also primary carcinoma of the liver occurs more frequently in men than women, and this is the universal opinion.

PATHOLOGY.

The liver is unique in its extraordinary powers of regeneration after trauma. In Mann's experiments on dogs[30] partial hepatectomy (four-fifths of the organ) was followed by complete regeneration in six weeks, and this reparative process was found to be accomplished by the hyperplasia of cells rather than by their hypertrophy. This remarkable capacity for regeneration in response to trauma and inflammatory conditions must always be considered in deciding on the malignancy, or potential malignancy, of a group of liver cells.

Local hyperplasia of liver cells may take several forms, and, as Ewing puts it, "all of these conditions occur with and without cirrhosis, and many of the simple hyperplastic processes lead through benign tumours into malignant neoplasms, thus complicating the task of separation into groups."

He makes three divisions of epithelial neoplasms of the liver: (1) Hepatoma; (2) Cholangioma; (3) Mixed tumours. A hepatoma is a solid parenchymatous tumour arising from liver cells; a cholangioma, which is the glandular type, arises from intrahepatic bile-ducts; while the third variety arises apparently from both liver cells and bile-ducts. From the point of view of gross anatomy they are "solitary or multiple, massive or nodular, and rarely diffuse". Microscopically he classifies hepatoma as: (*a*) Adenoma; (*b*) Adenocarcinoma; or (*c*) Carcinoma (solitary, multiple, or atypical). Cholangioma is classified as: (*a*) Adenoma (solid or cystic); (*b*) Adeno-carcinoma; or (*c*) Carcinoma.

Clinical Classification of Hepatoma (according to Ewing).—

a. Solitary adenoma, whose benign character is due chiefly to encapsulation.

b. Massive liver-cell carcinoma, which represents a more rapidly growing, atypical, and malignant form of the solitary adenoma (*a*).

c. Multiple liver-cell carcinoma, which includes the highly malignant, rapidly-growing tumours occurring in livers in which cirrhosis is either absent or slight.

d. Carcinomatous cirrhosis, where the tumour appears to be the direct sequel of, or essentially connected with, the cirrhosis.

Histogenesis.—Van Heukelom[23] was the first to show how "hypertrophic liver cords" developed into hepatoma, and this work was later elaborated by Goldzieher and Bokay.[18] The transition of nodular hyperplasia into multiple adenoma and multiple carcinoma has also been studied[33, 39], and the process sometimes demonstrated in the same liver. In a similar manner the various gradations between adenomatous and carcinomatous cholangiomas have also been noted to follow proliferation of the intrahepatic bile-duct epithelium.

As regards the mixed type of tumour, the process is not so definitely established, and is still in doubt. Muir[31] and Rolleston (quoted by Ewing) maintain that "typical hepatomas may produce canals resembling bile-ducts".

Sarcoma.—Primary tumours of mesoblastic origin are extraordinarily rare, and their exact histogenesis has never accurately been worked out. According to Ewing there is "somewhat scanty but direct evidence that both the stroma cells and the endothelium of the capillaries are susceptible to tumour growth". Many of the reported cases probably represent mistakes in diagnosis, possibly due to incomplete autopsies. Syphilitic lesions in infants (Rolleston[1]), and leukæmia (Ewing), are both potential sources of error. Histologically they may be grouped as: (1) Angio-sarcoma; (2) Alveolar sarcoma; (3) Spindle-cell sarcoma; (4) Round-cell sarcoma.

Incidence.—According to Jaffe, "approximately 48 true primary sarcomas of the liver have been reported to date" (1924). Clinically, they cannot be distinguished from carcinoma, and run a parallel, though more rapid, course.

Primary Melanoma of the liver "is a very difficult diagnosis to establish" (Ewing). Rolleston, in reviewing the reports of 9 cases, emphasizes the possible relation with the uveal tract, and mentions that in at least two cases very small uveal melanomas were found post mortem.

Sarco-carcinoma.—The occurrence of this composite tumour, associated with cirrhosis, has been reported by both Lubarsch[29] and Saltykow.[38]

Separate Formation of Sarcoma and Carcinoma in the Same Liver.—Jaffe refers to two cases observed by Dominici and Merle,[12] and Saltykow, respectively. To these he adds a full report of a third case of his own, occurring in association with cirrhosis of long duration.

Origin of Primary Carcinoma.—Opinion is fairly equally divided on the respective theories of the unicentric[26, 35, 48] and multicentric[10, 23, 43] origin of these tumours, and there is apparently no likelihood of an early decision on the question.

ETIOLOGY.

1. Cirrhosis of the Liver.—The importance of cirrhosis as a frequently associated lesion has been mentioned by almost every observer since the work of Sabourin. Yamagiwa gave its association with hepatoma as being 75 to 100 per cent, and for cholangioma 50 per cent.

While practically all writers concur on this point, there is no agreement on its rôle as an etiological factor. In this connection there are three possibilities: (*a*) The associated cirrhosis may be a coincidence; (*b*) It may follow the tumour formation; or (*c*) It may precede it. The frequency of its occurrence, noted so universally, prevents acceptance of the first theory. As regards the second, cases have been observed in which an advanced carcinoma was present in the absence of definite cirrhosis.[22] On the other hand Blumenau[4] in 1920, in an investigation on hepatic cirrhosis, found that primary carcinoma of the liver had occurred in 3·5 per cent of a series of 198 cases of death from cirrhosis. This relatively high incidence of primary carcinoma is an obvious argument in favour of the etiological influence of an antecedent cirrhosis.

Counseller and McIndoe[10] noted that the predominance of males in the sex incidence of primary carcinoma corresponds to that of cirrhosis, and concluded that "from 3 to 4 per cent of cases of cirrhosis, particularly of the portal type, will become carcinomatous". They believed also that cirrhosis is associated with almost all hepatomas, and though it does not appear to be so frequently observed in cholangiomas, this may be due to the insufficient number of recorded cases.

It is interesting to note that Fried[16], in giving his opinion that hepatoma is more frequent in males, cholangioma in females, gave as a possible explanation "the predominance of cirrhosis of the liver in men, and bile-duct infections followed by an inflammatory hyperplasia of bile-ducts in women".

The consensus of opinion[36, 47] appears to be in favour of cirrhosis being antecedent; a few writers consider it a sequel to the neoplastic process, while others believe that the cirrhosis and carcinoma are both end-results of a common stimulating factor.

2. Chronic Parasitic Infections.—The importance of chronic hepatic disease as a causal factor is emphasized by the relatively high incidence of primary carcinoma of the liver in other races that are prone to various parasitic infections.

Thus Pirie in South Africa (1921) refers to the marked frequency of schistosomiasis (i.e., hæmic distomiasis) in his cases, and suggests this as a definite causal factor in producing carcinoma of the liver, since it has been experimentally shown to give rise to cirrhosis. In this connection Fairley[15] (quoted by Fried) maintained that the associated cirrhosis is due not to the ova alone, but mainly " to the bilharzial toxin present in the blood-stream, which is filtered out by the liver ".

Smith, working in the Philippine Islands in 1926, where primary carcinoma of the liver is so common as " a definite disease entity " that it can readily be diagnosed, stated that " the cirrhosis, as far as is known, invariably precedes the tumour formation, and is commonly conceded as being due to chronic infections of intestinal origin, either bacterial or parasitic ".

Strong and Pitts in 1930, in their series of 9 cases, stated that 8 of these patients were Chinese who " came entirely from Kwantung, a southern province of China, where liver fluke (*Clonorchis sinensis*) is common, and where chronic diseases of the liver frequently occur " (hepatic distomiasis).

Jaffe quoted several authors who noted echinococcosis in association with the disease, while Ascoli[3] found that all his cases gave a history of syphilis, malaria, or alcoholism.

With regard to the etiology of the cirrhosis itself, many factors have been mentioned apart from the various parasitic infections. These include alcohol and cardiac disorders, while Karsner includes coffee, tobacco, and opium as playing an important part in its production.

3. Etiological Factors of Minor Importance.—Amongst these may be mentioned a history of hereditary cancer (and this was present in 4 of Eggel's cases), lues, and trauma. As regards the latter, Hicks[24] in 1929 recorded a case of encapsulated carcinoma in a man of 77, who gave a definite history of severe trauma in the liver region fifteen years previously. At the operation for excision of the tumour, this was found to arise from " a cirrhotic band two inches wide " in the left lobe of the liver, presumably in the site of the old injury.

EXTENSION AND DURATION OF THE DISEASE.

Extension.—Most observers seem to be agreed that intrahepatic metastasis is of common occurrence, this no doubt being a consequence of the rich vascular and lymphatic supply of that organ. Apparently there is very early invasion of capillaries, giving rise to intravascular thrombosis, and this in its turn, though not invariably, causes rapid dissemination of malignant nodules within the liver. (Incidentally, many observers advance this as an argument against the theory of multicentric origin.)

In some cases the process of thrombosis may reach the inferior vena cava and thus involve the heart. Ewing stated that distant metastases are not very frequent, but are most commonly found within the thorax.

This comparative freedom from metastasis, in spite of early thrombosis, may probably be a result of the extreme rapidity of tumour growth, and Karsner has commented on the usual absence of necrosis in the tumour thrombi, with consequent improbability of malignant embolism. On the other hand, he believed that distant metastasis occurs more frequently and with a wider distribution (due to vascular spread) than is commonly conceded.

Interestingly enough, Ewing quotes many authors who agree that these extrahepatic metastases may secrete bile.

Duration.—All workers (Counseller and McIndoe, Karsner, Hale-White,[20] Fried, et al.) refer to the shortness in duration of this disease. Karsner considered that the average duration is about six months, the exact time of onset being difficult to determine on account of pre-existing symptoms due to cirrhosis.

In Counseller and McIndoe's series of 5 cases the duration varied from 19 days to 3 years and 7 months. Hale-White stated that "after the appearance of a malignant tumour of the liver life is seldom prolonged over four months". Fried concluded from the literature that the disease "runs a rapid course and is rarely of more than three months' duration".

It has been maintained that the shortness of duration is due to the rich blood-supply of the organ. This not only provides ready access to the general circulation for the toxic products of the tumour, but also leads to early intrahepatic metastases with consequent interference with the metabolic functions of the liver—"the king of organs" (Boyd[5]).

Allbutt and Rolleston,[1] in their conclusion that the duration rarely exceeds six months, stated that this forms a striking contrast to secondary malignant disease of the liver, where the patient may often linger for a long while.

CAUSE OF DEATH AND ASSOCIATED DISEASES.

Cause of Death.—Death is usually due to a rapidly progressive malignant cachexia, but several observers have commented on the relative frequency of sudden death from severe intraperitoneal hæmorrhage, due to malignant erosion of a large vessel.

In some cases, however, as pointed out by Ewing, latent carcinoma has been found at the autopsy on patients who have died from other diseases.

Associated Diseases.—Tull[44] (1932), in an interesting study of 134 cases in Singapore, noted a frequent association with active pulmonary tuberculosis, and cholelithiasis, "but in none of these was the gall-bladder involved in the new growth".

SYMPTOMATOLOGY.

It is unfortunately true that primary carcinoma of the liver possesses neither a pathognomonic feature nor even a characteristic clinical picture. There may or may not be a history of vague gastro-intestinal symptoms, and the physical findings are always very variable, this probably depending to some extent at least on the mechanical effects of the growing tumour (Griffith[19]), and on its metastases in other organs. Clinically the usual picture

is simply that of portal obstruction of some kind, with its customary though varied manifestations.

According to Eggel's series of 164 cases, the chief symptoms appear in the following percentage incidence: Icterus, 61; ascites, 58·5; œdema, especially of the lower extremities, 41; splenic enlargement, 32; pyrexia, 14.

As regards the liver itself, Allbutt and Rolleston considered that this organ is usually enlarged and associated with local pain and tenderness, though rarely it may be reduced in size, owing to contraction of the coincident or antecedent cirrhotic tissue. Similarly in Tull's series, the liver was enlarged in 126 cases, but "definitely diminished" in 8. According to the former, the usual weight of the cancerous liver is about 125 oz., with extreme variations from 36 to 493 oz., though it is rare to find it weighing more than 200 oz. (The weight of the normal adult liver is 50 oz.) It was also their conclusion that the right lobe is more commonly involved than the left.

A very remarkable point is that though the typical anæmia and emaciation of malignancy usually develops *pari passu* with the new growth, rare cases have been referred to by Rolleston where the terminal exuberance of the neoplasm has been attended by a considerable gain in weight of the patient.

Enlargement of the spleen is an inconstant feature and variable in degree. If present it may be due rarely to metastasis, while Karsner believed that toxic factors together with general abdominal stasis contribute to its development.

It is rather surprising that definite splenic involvement is not more constant, when it is remembered that "even in health 25 per cent of the blood in the portal vein comes from the spleen" (Boyd), and some degree of portal obstruction must always be present, owing either to the neoplastic or cirrhotic elements, or to both. In any case splenic enlargement has usually only been noted post mortem, and it is doubtful if this feature could often be demonstrated clinically.

Recorded observations on the incidence of jaundice are interesting, in that, though often present, it is usually slight in degree[45] and late in onset. Thus Tull noted that "it is remarkable that one so often sees a liver actually riddled with new growth, and *no* jaundice". This forms a marked contrast with the prolonged dark staining so commonly found associated with secondary carcinoma of the liver, and it is possibly explained by the short clinical course of a primary neoplasm in this region.

The development of icterus may be attributed to mechanical factors, such as obstruction to the outflow of bile due to intrahepatic tumour nodules, or to the secondary involvement of the hilar lymph-glands, but also to the results of the cachexia and to the circulation of the toxic products of malignant growth.

DIAGNOSIS.

Most statistics on this subject are founded on observations at autopsy, and it appears obvious that the great majority of diagnoses are only made post mortem. In this connection Smith has pointed out that in tropical countries where primary carcinoma of the liver is a definite entity, it can be,

and is, readily diagnosed. Similarly, Strong and Pitts were able to make at least one correct ante-mortem diagnosis based on their previous experience with that class of patient. They stressed a point which they considered common and of diagnostic importance—namely, that the liver early becomes fixed, and "frequently enlarges upwards to a greater extent than downward", and that this feature may easily be missed if the liver is merely palpated below the costal margin. In one of their reported cases the dome of the liver was demonstrated clinically and radiographically to extend up to the second rib.

Brulé[7] (quoted by Counseller[10]) also insisted on the significance of fixation of the liver "so that it moves neither with palpation nor with respiration", and Tull observed that in 52 out of his 134 cases the dome of the liver was pushed up by the tumour "sometimes as high as the third rib".

Von Glahn[17] in 1924 remarked that on account of the undoubted association with cirrhosis any unusual clinical feature in such a case under observation should bring up the remote possibility of developing carcinoma. Thus if the cirrhosis were advanced to such a stage that a considerable decrease in the size of the liver would be expected, and if on the contrary the organ were enlarged or actually noted to increase under observation, there would thus be gained some slight evidence in favour of the rarer disease.

On establishment of a tentative diagnosis of carcinoma of the liver it is hardly necessary to stress once more the necessity of adequately excluding —as far as is possible—the presence of a remote primary neoplasm.

With regard to biochemical investigations, "the liver may be riddled with new growth and still function normally as judged by various function tests" (Tull, in 1932).

Again, clinically it would be impossible to differentiate a sarcoma from a carcinoma, but as regards pigmented growths the possibility of melanuria should be investigated.

OPERABILITY.

This aspect should always be considered, though unfortunately on account of the late development of symptoms, the rapid course of the disease, and its quick dissemination, operative measures can very rarely be practicable. Almost all the statistical details have been obtained from necropsy material and there are few records of operations for the removal of these tumours.

Keen[27] in 1889 had collected reports of 76 cases of operations on the liver for various conditions, including three primary carcinomata of his own, and concluded that "every case saving those manifestly beyond relief should be explored, and the later steps determined by what is found".

With this belief Thompson[42] in 1899 concurred, and noted with surprise the small operative mortality in the reports—6 deaths out of 38, and only 2 of these from hæmorrhage.

Anschütz[2] wrote a monograph on the subject from the operative standpoint in 1903, and both his and Thompson's work was considered by Yeomans[53]. He in 1915 was able to tabulate from the literature only 16 cases of operations for primary carcinoma of the liver. Out of these 16, 4 patients died from various causes within sixteen days, 6 patients had recurrences in periods varying from two months to eight years, while 6 patients were alive and well

from three to seven years subsequent to their operation. Griffith, in his review of 57 cases in childhood (1918), mentioned that laparotomy had been performed in only one of these, and that unsuccessfully; but considered that on account of the extreme gravity of the disease "it would seem justifiable to make such an effort at removal whenever in any way possible".

In 1923, at a meeting of the Royal Society of Medicine, 5 cases were discussed. Grey Turner presented particulars of an interesting case of excision of "an unusual type of hepatic adenoma" in a boy of 13, with recovery up to a period of twenty-two months after the operation. He gave a full description of his operative technique for partial hepatectomy, and mentioned that out of his long series of 14,923 operations he had only felt justified in performing the operation on two occasions. Garnett Wright[50, 51] described a successful removal of a primary hepatoma in a man of 60. The operation, which was "of a somewhat incomplete nature", had not been followed by recurrence (within two and a half years), which fact he attributed to "low-grade malignancy, if any". Philip Turner reported an excision of a large hepatic adenoma which had undergone necrosis, and caused such a severe intraperitoneal hæmorrhage as to simulate a ruptured ectopic gestation and to precipitate rapidly a fatal post-operative issue. Frank Kidd also mentioned a case of "a rare form of hepatic adenoma" in a female of 57, which simulated subacute appendicitis with abscess formation. An apparently successful operation was unfortunately followed by the death of the woman from heatstroke. Nitch gave a brief summary of a case in which he had removed a "carcinoma of an adrenal rest" from a woman of 54, followed by death from recurrence in twenty months.

Although none of these 5 cases was a primary carcinoma, yet it is reasonable to conclude from them and from the other cases cited above that if an apparently primary neoplasm of the liver is encountered during the course of a laparotomy undertaken with some other diagnosis in mind, due consideration must be given to the possibility of its removal.

Although, on account of the essential nature of this disease, accurate and early diagnosis is rarely possible, it should be aimed at, and a process of exclusion applied in cases that do not present a definite and true clinical picture. For, as Yeomans stated in 1915, "the only hope for improvement in results lies in the direction of earlier operative exploration in patients with a tumour in the right upper quadrant, in whom no primary growth can be found elsewhere".

In the case of typical solitary adenoma at least—where "the benign character is due chiefly to encapsulation and transitional forms to adenocarcinoma occur" (Ewing)—an adequate excision of such should prove successful, and its results may provide a striking contrast to the alternative of surgical inactivity.

CASE REPORT.

R. B. F., married man, 51 years of age. The patient was referred for a further opinion by Dr. W. S. McDougall and by Mr. A. T. Moon, F.R.C.S., of Wallington, Surrey.

HISTORY (June 15, 1933).—The patient had noticed a lump in his abdomen seven days previously. During this week he had had vague discomfort all over

the abdomen, especially when lying on the right side. The discomfort had become an aching pain, both front and back, for two days. He said he had been examined for an insurance policy and passed as a first-class life on May 9, but apparently the abdominal examination was most cursory. There was no history of any previous illness for which he had been attended by a doctor since childhood complaints. He had never suffered from syphilis or lived abroad.

On Examination.—The patient appeared a very fit man, not older than his years. Apart from the local abdominal condition, no other abnormalities were detected by any one of us. On abdominal examination a very large mass was both seen and felt occupying the centre and right side of the abdomen (*Fig.* 421). In the mid-line it extended from about an inch below the xiphisternum to about three inches above the symphysis pubis. Towards the left it extended to the mid-clavicular line, stopping short of the costal margin by about half an inch. To the right it extended well beyond the right mid-clavicular line into the right lumbar and right iliac fossa regions. Its shape appeared roughly that of a Rugby football, its main axis being directed from the left costal margin downwards to the right iliac fossa. Its surface appeared smooth, the edges shelving off with evidence of gross nodularity. In consistency it was very firm, with no sensation of fluctuation at all. The tumour moved very freely on respiration, and from side to side on manipulation. On percussion the tumour was quite dull, except at the right lower portion, where the colon slightly overlapped it. Above and to the left stomach resonance was easily detectable, causing a definite area of resonance between the tumour and the splenic dullness. The liver dullness extended from the upper border of the 5th rib in the right clavicular line downwards to just below the right costal margin. At this level the percussion note became slightly less dull for about one finger-breadth, and then again became quite dull over the tumour. This small zone of impaired resonance between the normal liver and the tumour was presumably due to the fact that the duodenum, as shown by the X-ray examination, was lying behind the liver in this situation. Because of this physical sign, differential diagnosis from a pancreatic tumour was made difficult. There was no suspicion of ascites and no other abnormality could be detected in the abdomen. Rectal examination revealed no abnormality. The testes and prostate were normal. The urine contained no abnormality and the Wassermann reaction was negative.

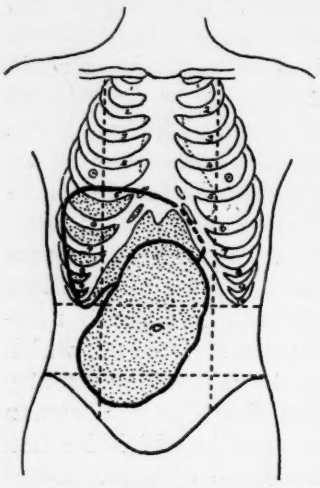

Fig. 421.—Diagram showing position occupied by tumour in abdomen.

An X-ray examination, including barium meal and barium enema skiagrams was kindly undertaken for me by Professor Morison. He reported as follows :—

Chest.—Revealed nothing abnormal ; the levels of the diaphragm were normal, and its movements were free and unrestricted on both sides.

Barium Meal.—The body of the stomach was displaced to the left ; the pyloric end and duodenum were displaced upwards. Nothing abnormal was detected in the stomach, the distortion being due to pressure from outside. The small intestine was displaced downwards.

Barium Enema.—The whole colon was outlined, the transverse colon being displaced downwards, the ascending portion of the transverse colon and splenic flexure were displaced to the left ; nothing abnormal was detected in the colon, the displacement being due to the pressure from outside.

Findings.—The X-ray examination indicates the pressure of a large tumour which is displacing the body of the stomach to the left, the pyloric portion of the stomach and first part of the duodenum upwards, the descending portion of the duodenum to the right, and the transverse portion of the colon and small intestine downwards. The examination suggests a pancreatic tumour (which agreed with the clinical diagnosis).

Definite evidence of the hepatic origin of the tumour could probably have been determined by a hepatogram.*

Operation (June 20).—One hour before the operation the patient was given a hypodermic injection of one Roche's ampoule containing omnopon gr. $\frac{2}{3}$, scopolamine gr. $\frac{1}{150}$. A spinal anæsthetic was skilfully administered by Dr. Ronald Jarman, 16 c.c. of 1–1500 percain being injected between the 3rd and 4th lumbar vertebræ. The patient was placed in the prone position for six minutes before being turned on to his back, all the time being in a slight Trendelenburg position. Nitrous-oxide-oxygen general anæsthesia was given by the McKesson apparatus. No chloroform or ether was used.

A long right paramedian incision revealed a large tumour arising entirely from the left lobe of the liver, which was displaced downwards and towards the right. The right lobe appeared quite normal, except for a small white spot about the size of a pin's head one inch to the right of the falciform ligament, and close to the antero-inferior edge. A careful search of the entire abdomen, including renal and supra-renal areas, failed to reveal any primary focus, and it appeared probable that the case was one of primary carcinoma of the liver, and it was decided to attempt removal.

Between the right lobe of the liver and the area in the left lobe occupied by the tumour was an interval of apparently normal left lobe of liver about one and a half inches in thickness.

Keeping close to the line of the falciform ligament, a series of catgut sutures, using double thickness No. 2 chromic catgut, were passed through the whole substance of the liver, and firmly tied. Each succeeding stitch slightly overlapped the preceding one, and working from below and above alternately, the tumour-bearing area, together with a good inch of apparently normal liver, was removed. This meant that practically the whole of the left lobe of the liver was removed. Little hæmorrhage occurred, several large arteries and veins being recognized and clipped before being cut across. To each of these a separate ligature was applied. A raw area some 7 by 3 in. remained which was still further drawn together by a thick running catgut suture, which incorporated the large hæmostatic sutures in its course. Complete hæmostasis was thus secured, and only a very small area about 3 in. by $\frac{1}{2}$ in. remained. The minute spot to the right of the falciform ligament was also removed with a small wedge of liver tissue. A cigarette drainage tube was inserted and the abdomen closed. Shock was inconspicuous. Apart from a slight temperature for a few days, the patient made an uninterrupted recovery, and has remained apparently perfectly well ever since.

Pathological Report.—The specimen (*Fig.* 422), when first removed, and still engorged with blood, weighed 5 lb. It was submitted to Dr. L. M. Hawksley, Pathologist at the Cancer Hospital, who reports as follows:—

An ovoid mass of tissue, $8\frac{1}{2} \times 6\frac{1}{2} \times 4$ in., weighing 3 lb. 11 oz.; liver substance obvious on the cut surface, the remainder showing a diffuse mottling of ill-defined nodules of new growth, which on section is seen to infiltrate the entire tissue, except for about 1 in. of apparently normal liver substance to the right of the tumour mass; the nodules range in size from that of a pin-point to one 2 in. in diameter, with cystic change.

Microscopic Examination.—Little variation in structure has been found in the numerous pieces taken for section. The thin fibrous tissue stroma is scanty, and it is a matter of difficulty to find even a few liver cells. The bulk of each section is made up of an epithelial tumour formed of tall and extremely regular columnar cells in tubular and glandular arrangement. Branching papillary processes project into cystic spaces, which contain also albuminous coagulum, and there is evidence of deposition of cholesterin and of calcium salts. (*Figs.* 423, 424.)

Nodule from Right Lobe.—A small area shows a similar, but less advanced, condition.

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* An intravenous injection of 20 to 25 c.c. of thorotrast daily for three days causes a deposit of thorium in the liver, spleen, and lungs, which then become opaque to X rays. Enlargements of liver and spleen or filling defects of these organs, or the presence of tumours in them or the lungs, are demonstrable. This method was not available in this case.

The histological features of the tumour indicate that it is an adenocarcinoma of the intrahepatic bile-ducts, which has probably arisen in multiple foci representing a transition from simple adenomata. In view of the radical removal of the tumour-bearing tissue, the prognosis would seem to be influenced entirely by the tendency seen to the development of the same condition in the right lobe.

FIG. 422.—Tumour from in front, cut to display interior. (× ⅔.)

Professor Kettle was kind enough to examine the sections, and he confirms the pathological diagnosis in the following words :—

" I have been very interested to examine the sections of your liver tumour and agree with you as to its possible origin. The small nodule looks to me much more like a primary growth than a secondary deposit, and, although the main mass would do for an adenocarcinoma almost anywhere, I take it that it is probably a bile-duct carcinoma. I suppose there must be something disturbing the bile-duct epithelium through the whole liver, and it is quite likely that the big mass may represent several primary foci which have coalesced."

FIGS. 423.—Photomicrograph of a portion of the tumour. Immediately beneath the capsule of the liver the transition from simple dilatation of bile canaliculi to extensive proliferation of epithelium in single layers is seen. Throughout the greater part of the tissue the regular characters and adenomatous structure prevail. (× 40.)

FIG. 424.—An area in which a papillary type of overgrowth has developed. In other parts the tumour tissue is of a more solid type, and small areas show calcium deposition and cyst-like spaces in which there is evidence of an accumulation of cholesterin. (× 40.)

SUMMARY AND CONCLUSIONS.

1. Primary carcinoma of the liver is a rare disease, occurring chiefly in males, mainly between 40 and 60, though no age is exempt.

2. It has an average incidence of not more than 0·3 per cent of all autopsies.

3. There are two main types of tumour: (*a*) Hepatoma or carcinoma of liver cells; (*b*) Cholangioma or carcinoma of intrahepatic bile-ducts.

4. Sarcoma of the liver occurs with even greater rarity, and clinically is indistinguishable from carcinoma.

5. The most commonly associated condition is cirrhosis, which is probably antecedent, and is indubitably related in etiology to carcinoma.

6. The relatively higher incidence in some other races is most likely attributable to various local parasitic infections of a chronic nature with consequent cirrhosis.

7. Diagnosis is difficult, though not impossible, and there are no pathognomonic features.

8. Fixation of the liver with upward enlargement (which may be demonstrated clinically, and confined radiologically) is sometimes present, while unusual features in a case of cirrhosis under observation may act as a signpost towards the correct diagnosis.

9. The prognosis is in all cases of the most extreme gravity, the disease running a rapid clinical course with an average duration of less than six months. In certain selected cases, however, it is not entirely without hope.

10. Intrahepatic metastasis is common. Extrahepatic metastases are less commonly encountered, and the mode of dissemination is almost certainly via the blood-vascular system.

In view of the liability to metastases, preliminary radiological examinations should be carried out.

11. The disease may be encountered during the course of a laparotomy (either exploratory or following a mistaken diagnosis). In each case a decision whether a radical partial hepatectomy can or cannot be undertaken must be made.

12. A case of massive cholangioma (carcinoma arising from intrahepatic bile-ducts) is fully described with details of a successful operation. Points of interest to be noted are:—

a. There was no general enlargement of the liver in an upward direction; all the tumour enlargement had occurred downwards.

b. The tumour was freely movable both on respiration and from side to side on movement and on palpation.

c. Neither jaundice nor ascites was present.

d. The right lobe of the liver was almost unaffected, except for a minute nodule, microscopy of which led to an accurate diagnosis of the real nature of the main mass, which occupied almost the whole of the left lobe of the liver, and had grown to nearly twice the total weight of a normal liver.

e. The operation was not of great technical difficulty, and the patient made an uninterrupted recovery, and has remained well to the time of writing this article (January, 1934—seven months).

My thanks are due to Professor Kettle, Professor Morison, and Dr. L. M. Hawksley for permission to publish their reports, and also to Dr. W. Freeborn for his help with the extensive researches into the literature.

Note.—Since this article went to press the patient had a febrile attack with slight jaundice, from which he recovered, but on subsequent examination was found to have marked enlargement of his liver with ascites (March, 1934).

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SHORT NOTES OF RARE OR OBSCURE CASES

SPHEROIDAL-CELL CARCINOMA OF BREAST: EXTENSION OF GROWTH WITHIN THE PERIMYSIUM.

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Considerable practical, as well as theoretical, importance attaches to the method of extension of carcinoma of the breast. The conceptions of Handley with regard to lymphatic permeation are well known, and to some extent regulate current operative practice in the removal of the pectorals, to ensure removal of the fascial planes in which lymphatics travel.

Histological evidence of the tendency of carcinoma to spread along channels, such as lymphatics, blood-vessels, and inside the sheaths of nerves, is quite definite. Direct involvement of voluntary muscle is, however, rare, and even when a carcinoma is clinically attached to the muscles, microscopic evidence of their invasion is very frequently lacking.

The very unusual picture shown in the accompanying illustrations (*Figs.* 425, 426) indicates direct permeation within the perimysium.

History.—The history of the patient, a female, aged 54, married with one child of 20, was as follows:—

1917.—Suspected pulmonary tuberculosis.

1929.—Carcinoma of right breast: radical amputation.

1931.—Laryngitis; cause never definitely diagnosed.

1932.—Marked deterioration in general health, with difficulty in swallowing, sore throat, and cough.

1933.—Two secondary deposits in the scalp removed. During the last twelve months the patient lost 1½ stones in weight. Persistent nausea and vomiting.

On Examination.—When first seen on June 8 there was no evidence of any disease in the nose, throat, or neck. The vocal cords moved freely, the arytenoids were normal, and there were no enlarged cervical glands. There were two secondary deposits on the front of the chest, one over the sternum near the opposite breast, and the other at the level of the 9th rib in the mid-axillary line. These deposits were not attached to the skin, but clinically were fixed to the chest wall.

X-ray examinations showed no œsophageal obstruction and no metastases in the lungs, but some adhesions in the region of the diaphragm on both

FIG. 425.—Carcinomatous infiltration of voluntary muscle early stage. Carcinoma cells are present in the centre of muscle fibres. (× 64.)

FIG. 426.—Carcinomatous infiltration of voluntary muscle, late stage. The muscle fibres are replaced by cylinders of spheroidal-cell carcinoma; the perimysium is intact. (× 64.)

sides, and marked thickening of the pleura on the left side. This may possibly have been due to tuberculosis.

OPERATION.—The two tumours on the chest wall were removed, and a radium jacket was applied to the back and front of the chest on the left side from the supraclavicular region down to the spleen. Intermittent irradiation was given for a period of about three weeks, 100 mgrm. to the front hest, 80 mgrm. to the back, making in all 20,368 mgrm.-hours, and, except or a post-irradiation depression, the general condition improved and the vomiting, which was considered functional, ceased.

The illustrations (*Figs.* 425, 426) are of the tumour attached to the chest wall. It will be seen that the earliest deposits appear to be in the centre of the muscle fibre, and that there is later extension leading eventually to a column of growth in a cylinder composed of perimysium.

It is noteworthy that this is a late secondary deposit. As a rule, in earlier deposits the reaction of the voluntary muscle is one of sarcolemmal proliferation and absorption of the muscle fibres, producing not infrequently the so-called 'muscle giant cells'. There is no suggestion that the lymphatics of muscle travel inside the perimysium.

The case was under the care of Mr. Stanford Cade, to whom I am indebted for the history. The illustrations are the work of Mr. S. A. Sewell.

OSTEOCLASTOMA OF FEMUR: EXCISION: RECONSTRUCTION OPERATION.

BY ST. J. D. BUXTON,

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THIS case is reported to demonstrate a reconstruction operation after removal of a giant-celled myeloma (osteoclastoma) with the lower end of the femur when local removal of the tumour was not possible.

B. S., female, aged 34, married woman, was admitted to hospital in August, 1931, with a pathological fracture into the left knee-joint.

X-RAY EXAMINATION.—This showed a tumour affecting both condyles of the lower end of the femur. The fracture extended into the knee-joint through the intercondylar notch and through the lower end of the shaft transversely across the bone.

OPERATION (August, 1931).—The lower end of the femur with both condyles containing the tumour was removed. A round hole, $\frac{1}{4}$ in. deep, was made in the upper surface of the tibia, and the cut surface of the shaft was inserted into this. Two bone-pegs were inserted to hold the shaft in place, and the patella was fixed on the front after removing the articular cartilage. The portion of bone and tumour removed is shown in *Fig.* 427.

The pathologist reported that macroscopically and microscopically the tumour is a giant-celled myeloma (osteoclastoma).

After convalescence in plaster and a caliper, the patient found the limb satisfactory. She is now able to walk as much as she wishes, wearing a high boot to compensate for the $2\frac{3}{4}$ in. of shortening of the limb.

FIG. 427.—Showing lower end of femur after removal. The tumour tissue can be seen after the condyles have been further separated through the line of fracture. ($\times \frac{3}{4}$.)

FIG. 428.—Skiagram taken on Aug. 14, 1931, prior to operation. The destruction of bone by the tumour is shown and the line of fracture both transversely and into the joint is seen.

Fig. 428 shows the tumour and pathological fracture prior to operation (August, 1931), and *Figs.* 429, 430 show the condition in June, 1933, when

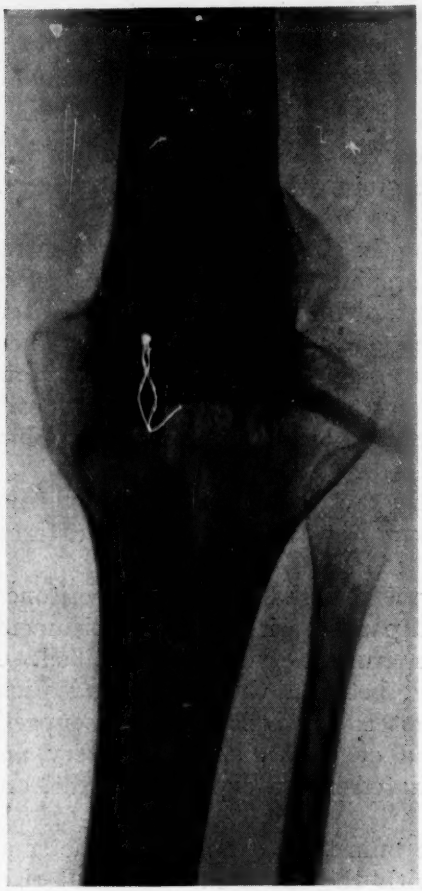

FIG. 429.—Antero-posterior skiagram after reconstruction (June 28, 1933).

FIG. 430.—Lateral skiagram after reconstruction (June 28, 1933).

union is firm. It will be noted that the lower half of the patella is united firmly, but the upper half is standing away from the femur.

TWO CASES OF ILIOPSOAS BURSITIS.

BY J. S. RAMAGE and G. BROWN MORTON, STOKE-ON-TRENT.

As this is a comparatively rare condition, and one which may cause considerable difficulty in diagnosis, the following two cases are perhaps worthy of record.

Normally there exists between the iliopsoas muscle and the ligamentum iliofemorale, a large bursa which frequently communicates with the synovial cavity of the hip-joint. The bursa lies in the line of the external iliac and

femoral arteries and is separated from them by the iliopsoas muscle. It will be readily understood that when it is enlarged and filled with fluid the overlying structures will be pushed forwards, and, on account of the relationship with the arteries, inguinal aneurysm will be closely simulated. As a matter of fact, in the cases here reported this resemblance was very close, and in the first case operation was carried out on a provisional diagnosis of aneurysm.

Case 1.—Male, aged 60 (1926). Shoesmith.

HISTORY.—For the past eighteen months the patient had noticed a gradually increasing swelling in his right groin, which had recently begun to interfere with his work as a shoesmith.

ON EXAMINATION.—There was a swelling the size of a large orange centred midway between the anterior superior iliac spine and the symphysis pubis, and lying chiefly above Poupart's ligament. The swelling was moderately tense, smooth, and rounded, and had ill-defined but regular margins. There was pulsation, apparently of expansile nature, synchronous with the arterial pulse. The pulse below the swelling was smaller than that of the opposite limb. No tenderness present. The range of movement of the right hip-joint was slightly diminished.

In view of these clinical findings, plus the fact that there was no evidence of syphilis or spinal caries, a provisional diagnosis of aneurysm of the external iliac artery was made.

OPERATION.—The external iliac artery was exposed by the extraperitoneal route, using an incision one inch above and parallel with Poupart's ligament. The external iliac vessels and the anterior crural nerve were identified. A large tense fluctuant swelling was defined between the iliacus and psoas muscles, pushing the nerve and blood-vessels forwards against Poupart's ligament. The nerve was gently retracted outwards, and the artery and vein inwards. The swelling was then aspirated by an exploring needle, and the diagnosis of iliopsoas bursitis made.

As much as possible of the wall of the bursa was excised, and the small posterior portion, which communicated with the hip-joint, was cauterized with carbolic acid. The wound was closed without drainage.

Convalescence was uneventful.

Case 2.—Male, aged 72 (1932). Gardener.

HISTORY.—Six months prior to admission to hospital this man noticed a swelling in his left groin. This caused no inconvenience whatsoever. Within the last few weeks, however, the swelling increased so rapidly in size that he called in his doctor.

ON EXAMINATION.—A swelling in the left groin was revealed. This was of elongated oval shape, about the size of a large lemon, and situated chiefly below Poupart's ligament, its axis being in the line of the external iliac and femoral arteries. The swelling was moderately tense, its outline regular, and its margins were rather ill-defined. Expansile pulsation synchronous with the arterial pulse was present. There was a slight impulse on coughing felt in the part of the swelling below Poupart's ligament. The range of movement of the left hip-joint was normal. There was no evidence of syphilis or spinal caries.

In view of our knowledge of the previous case, a diagnosis of iliopsoas bursitis was made.

OPERATION.—The external iliac artery was exposed as in the operation for *Case* 1, and the inner end of the incision was carried downwards along the axis of the swelling so as to expose the femoral sheath for a distance of two inches. A practically similar state of affairs was found as in *Case* 1. The swelling extended rather further below Poupart's ligament and had a biloculated formation (*Figs.* 431, 432). The larger of the two sacs was actually above Poupart's ligament, although the external appearance had suggested the converse. The impulse on coughing was no doubt due to a fluid wave from the larger to the smaller sac. No communication with the hip-joint could be demonstrated.

The same surgical treatment was adopted as in *Case* 1.

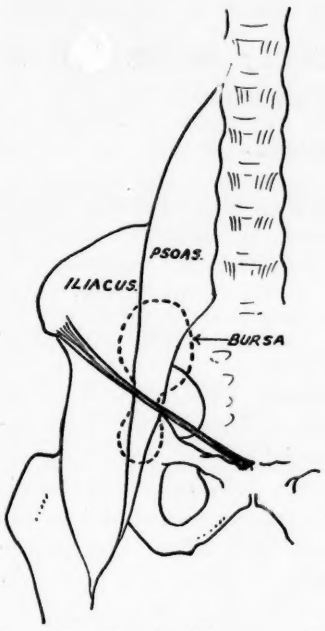

FIG. 431.—*Case* 2. Diagram to show approximate extent of bursa.

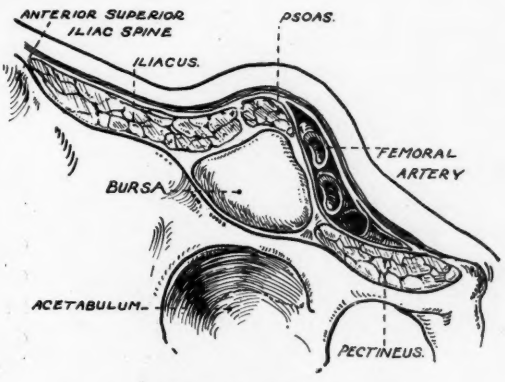

FIG. 432.—*Case* 2. Diagram to show relations of bursa.

COMMENTS.

In each case a definite cause for the enlargement of the bursa could be found—namely, in *Case* 1 the patient was a shoesmith, and was in the habit of holding the horse's hoof in the right groin while hammering in the nails. In *Case* 2 the patient had been doing a considerable amount of digging in a hard clay soil and was accustomed to strike the spade with his left foot. The swelling in the groin had developed only since his constant work in this hard soil. Factors of a chronic irritative nature were therefore present in each case, and were no doubt the cause.

The rarity of iliopsoas bursitis is no doubt due to the depth of its situation and corresponding freedom from trauma. When it does develop, its anatomical situation makes the diagnosis extremely difficult. It can therefore be easily understood that a considerable enlargement of the bursa with the transmitted pulsation of the overlying artery can closely simulate inguinal aneurysm.

In *Case* 2 the additional factor of the impulse on coughing, while against inguinal aneurysm, added to the difficulty of diagnosis, as the possibility of femoral hernia had to be considered. Fortunately in the light of previous experience a correct diagnosis was made.

We are indebted to Mr. Harold Hartley, under whose care *Case* 1 was, for permission to include it in this report.

A CASE OF MARCH FOOT (PIED FORCÉ) WITH SIGNS OF OLD AND RECENT INJURY.

By W. B. R. MONTEITH, Bourne.

This case of pied forcé, showing evidence of simultaneous old and recent injury, seems of sufficient interest to justify publication, following on the article by H. Dodd in the July, 1933, issue of The British Journal of Surgery.

Fig. 433.—March foot.

In August, 1932, a trainee at the Bourne Government Instructional Training Centre, employed in quarrying, came to me complaining of pain and tenderness over the left metatarsal region of two or three days' duration. There was no definite history of injury. I X-rayed the foot, and the film (*Fig.* 433) shows the following state: In the second metatarsal an oval 'tumour' of rarefied bony structure; but the line of a fracture can be seen across the centre of the swelling, and there is some periosteal thickening of the shaft. A recent fracture is seen in the same position in the third metatarsal. The first or earlier fracture had been unnoticed and untreated, and this certainly accounted for the excessive callus formation.

The case was treated as a fracture, but unfortunately the subsequent history is unknown, as trainees have to leave the Training Centre when incapacitated.

REVIEWS AND NOTICES OF BOOKS.

Die spezielle Chirurgie der Gehirnkrankheiten—Die epileptischen Erkrankungen (Vol. 49a of *Neue Deutsche Chirurgie*). Vol. 49a, by Prof. FEDOR KRAUSE and Dr. HEINRICH SCHUM. Pp. 520 + xx, with 112 illustrations and 1 plate. Also Vol. 48 (edited by F. KRAUSE). Written by Prof. N. GULEKE, K. BOSHAMER, C. T. WILLICH, G. JORNS, G. BRÜHL, E. HARMS, and H. SMIDT. Pp. 735, with 43 illlustrations. 1930 and 1931. Stuttgart: Ferdinand Enke. Vol. 48: Paper covers, RM. 86.40; bound, 89.10. Vol. 49a: Paper covers, RM. 70.20; bound, 72.90.

THE great series of special monographs which goes under the name of the "Neue Deutsche Chirurgie" is a library which commands the greatest respect. Founded by Paul von Bruns, and its general editorship carried on by Professor Küttner, of Breslau, it is reinforced by four or five volumes a year. The volumes under review are concerned with special neurosurgical problems and are additional to the two published some years ago under the title of *Allgemeine Chirurgie der Gehirnkrankheiten*. All these volumes have been produced under the special editorship of Fedor Krause, who is, in addition, the part-author of Vol. 49a, *The Epileptic Maladies* (by Professor Krause and Dr. Schum). We will deal with this first.

Krause's large book on the surgery of the brain and spinal cord, translated into English, and appearing in three-volume form in 1910, brought him into touch with all those interested in the surgery of the nervous system, and remains as a lasting memorial of the surgery of that period. It 'dates', as the saying is, more than most surgical works, because neurosurgery has advanced more rapidly than any other branch of surgery during the past two decades. But the work is still important and bears testimony to the courage, the honesty, and the industry of its author, who represented the best thought of his period. To the present volume on the epilepsies the authors have brought the same unflagging zeal, but it is not in its plan a personal record, and undoubtedly in that form it would have been more valuable than is actually the case. It is, instead, a most closely documented record of publications on the subject, and the author must be congratulated on his choice of commentators in a literature which is probably larger than that of any other disease. It begins with historical and statistical sections which are models of their kind. The authors discuss the frequency of epilepsy after head injury, and this part contains a mass of useful information. They place the percentage incidence at between 25 and 30 per cent after bullet wounds, and think that is very rare in civil life. The reader is guided skilfully and fairly through the various percentages given by other writers. Under the title of "blood- and brain-pressure during the attack" Krause describes a post-operative fatality of his own with the coloured illustrations very well reprinted from his earlier work. He mentions Foerster's belief of a pre-epileptic vasomotor constriction and shrinkage of the brain up to the moment of the seizure, but Krause and Schum have not been greatly impressed by blanching of the exposed cortex before an attack is launched. They agree that the swelling and congestion seen during the seizure are but a local representation of a general cyanosis. In the chapter on etiology they describe the hyperventilation method of Foerster for inducing an epileptic attack. Foerster thought that convulsions could be made to occur in 40 per cent of cases, but a number of other workers were unable to produce them in anything like so large a proportion of their subjects. All the published figures are given and a brief discussion follows of the possible reasons for the success of the method.

A good section follows on birth and infantile injuries, and indeed every possible

cause of epilepsy is dealt with up to the incidence of epilepsy in brain tumours and its dependence on the site of the neoplastic lesion. There are 938 references at the end of the etiological section, and this is actually very valuable because the title of each paper is printed in full. The pathological part is well illustrated with microphotographs of Professor Ostertag's sections and Spielmeyer's work on the cornu ammonis, and the influence of vascular changes in bringing about focal degenerations is well described. More figures of glial alterations in large-scale pictures would have been welcome here.

The surgeon turns with especial interest to the last section of the book, "Physiologische Bemerkungen", for in this Krause describes his method of cortical stimulation. In a large-scale chart he records the motor points as observed in 142 patients whose Rolandic areas he has stimulated by the unipolar method. One reads with interest of Krause's conversations with Hitzig and of his reason for preferring the faradic to the galvanic current. Precise details are given of Krause's method of stimulation, current strength, and narcosis; it is surprising that he is not more favourable to local anæsthesia. Finally, there are adequate descriptions of stimulations of the general sensory and visual cortex, with remarks on the other special senses.

The reader closes the book with the feeling that here is gathered together all that is best of the world's thought on the various forms of epilepsy, and great credit is due to the guides who have led the reader so surely through such a maze. No English monograph exists which at all resembles it, for the English genius is more individual and more personal, and English readers may regret the care with which its authors have refrained from more passionate self-expression. Nor does the book contain a well-detailed account of local cortical excisions, and we should have welcomed Krause's mature opinion upon their results.

Vol. 48, which is of a quite different kind, must not detain us long. Its sections are written by several authors. All of these are excellent, with numerous original and striking illustrations. The sections deal with affections of the meninges (by Professor Guleke), cerebral softening and vascular degenerations (by Professor Boshamer), brain abscess (by Professor Willich), and a very well written article on otological and rhinological brain complications by Gustav Brühl, of Berlin. This last is what reviewers love to call a "veritable mine of information", and in this case the phrase is entirely applicable and true. Several sections by Hans Smidt, of Bremen, on vascular affections (sinus thrombosis, subdural hæmatoma, aneurysms) bring the volume to a close.

Human Embryology and Morphology. By Sir ARTHUR KEITH, M.D., F.R.S., LL.D., D.Sc., F.R.C.S., Master of the Buckston Browne Research Farm. Fifth edition. Medium 8vo. Pp. 558 + viii, with 535 illustrations. 1933. London: Edward Arnold & Co. 32s. 6d. net.

BOOKS written by Sir Arthur Keith are always interesting, and his *Human Embryology and Morphology* has made a place among medical text-books which is unique. Keith approaches embryology from a different standpoint from that which is generally adopted. He begins the description of a system or organ by giving a brief outline of its evolution and comparative anatomy. This is followed by a short account of its development in the human subject. He has endeavoured to provide a concise account of human development which will be useful to students who are to become practical physicians and surgeons rather than to provide advanced students or anatomists with a complete account of recent research work. A treatise of the latter type could not at the present time be adequately dealt with in a single volume, nor could it be accomplished by a single individual. Keith has, however, introduced a new feature into the fifth edition: he has attempted to indicate the lines along which research is tending, by giving a selected list of references to recent work on each system and region, with short explanatory notes which follow his description in the text.

Some processes of development—more especially the histological changes which take place in the development of blood and lymph and in the growth of tissues such

as cartilage, bone, and nervous tissue—we should like to have seen treated in greater detail, both with regard to the text and in the technique of the illustrations. At the present time this is especially desirable in view of the increased interest which is being taken in the results of experimental embryology and tissue-culture—for example, the relation of the normal processes of cell production and growth to heredity, certain morbid conditions of the system and tissues, the growth of tumours, and the repair of injuries to bone. In many cases where recent work is at variance with old-established doctrines, the reader would be glad to have some comments or discussion on the points at issue—for example, the rôle played by the periosteum and osteoblasts in the formation of bone. This function has been challenged by both British and French authors. Is the surgeon to be guided in his methods of treatment by the more recent doctrine of the non-participation of the periosteum in the formation of bone, or is he to hold on to the older views? A brief discussion of the pros and cons of this and other questions would have been most valuable.

The book is very clearly written and the numerous illustrations are a valuable help to the comprehension of the descriptions in the text. Some excellent new illustrations have been added in this edition, and we draw attention especially to the type of drawing which on account of its being an attempt towards a faithful representation of reality is so much more convincing than a diagrammatic figure, which may be very misleading. We should like to mention especially *Fig.* 359, the endothelial lining of the heart in a 4th week human embryo (Veit and Esch), and *Figs.* 428 and 429, representing models of the genital system of the female human fœtus at the 7th and 10th weeks of development (R. H. Hunter). Modifications of original drawings, on the other hand, such as in *Figs.* 18 and 27, are not permissible, and may give rise to a wrong impression. Again, such a diagram as *Fig.* 75, which has obviously not been drawn from a dissection of the part, represents the internal intercostal nerve superficial to the internal intercostal muscle instead of deep to it, and affords an excellent example of the liability to error that occurs in any attempt to reconstruct nature on preconceived ideas or prevalent but incorrect notions. In reviewing the book as a whole, however, such faults as we have drawn attention to appear trivial, and one is most favourably impressed by the wonderful way in which an extensive subject has been tersely described and illustrated within the limits of a single volume, every page of which is interesting and informative.

Fractures. By PAUL B. MAGNUSON, M.D., Associate Professor of Surgery, Northwestern University Medical School, Chicago. Medium 8vo. Pp. 466 + xx, with 317 illustrations. 1933. Philadelphia and London: J. B. Lippincott Company. 25s. net.

THIS volume sets out to meet the needs of "the man who first sees a fracture", and after reading it one cannot come to any other conclusion than that the author has successfully arrived at his object. If the author's claim for it to be judged as a volume of personal experiences be admitted, criticism of it as a mirror of modern treatment of fractures is of little value; but if the general lines of treatment are compared with those in vogue in this country, it is apparent that the author places more reliance upon the use of wooden splints than has been customary here for the past fifteen or twenty years. The chapters on the principles of repair and of treatment are marked with sound common sense and are clearly the outcome of personal experience. A good deal of space is devoted to the general principles of operation on fractures. In our judgement this is superfluous if the book is for the use of general practitioners, and the pages devoted to operations scarcely suffice to provide a practical guide to anyone who has to undertake such operations. Again, where space is allotted to operative detail the selection of subjects dealt with scarcely follows any logical sequence, for we have a fairly complete account of the operative treatment of old fractures of the os calcis and innumerable operations for the correction of a fracture of the neck of the femur, yet no description is given of an operation for fracture of both bones of the forearm "because this is a formidable procedure".

The book is profusely and beautifully illustrated; in fact, it teaches more by its figures and pictures than by its letterpress. A certain number of the illustrations are scarcely worthy of production—for instance, the Sinclair skate, which has surely been superseded by the ice-tong caliper and the Steinmann needle, just as these have yielded place to Kirschner's wire; though in this respect the author has an opinion which may not be generally shared—his preference for the ice-tong caliper—and this for what we consider to be a completely inadequate reason—that it does not involve drilling through the bone.

Destructive criticism of this kind is not difficult in regard to any book which is a record of personal experience and opinion, yet, in spite of minor defects of this nature, this book can be recommended as a useful guide to any house surgeon setting out along the thorny path of fracture treatment, as well as to anyone who has had years of experience in this subject, for often the latter will find its perusal not devoid of suggestion and instruction.

Intracranial Tumours. By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. Royal 8vo. Pp. 475 + xxiv, with 155 illustrations and coloured plates. 1933. London: Baillière, Tindall & Cox. 35s. net.

THOUGH this book is primarily a clinical study of the many pathological varieties of intracranial tumour, its outstanding feature is that Professor Bailey has arranged his material so as to set forth the evidence in support of the belief that a knowledge of the pathological nature of a cerebral tumour is of the utmost importance as a guide to its correct treatment. By approaching the subject from this aspect he has not only managed to throw fresh light upon many intricate problems of diagnosis, but has also drawn from his correlated clinical and pathological studies many deductions which are of value in prognosis. Though the localization of a cerebral tumour may still present considerable difficulty, modern aids to localization have reached such a degree of accuracy that the nature of the lesion becomes a matter of even greater importance than its position.

The first few chapters deal with the anatomical and physiological considerations which underlie the syndromes presented by cerebral lesions, and these are followed by a series of chapters every one of which is devoted to a single pathological entity. Accompanying the pathological picture is a description of the signs and symptoms which indicate the site of origin of the tumour. While the acoustic and hypophysial tumours naturally lend themselves to such treatment, it is most interesting to see how Professor Bailey has managed to associate the various forms of glioma with the localizing syndromes of their usual site of origin. For example, with the medulloblastoma comes the description of the syndrome of the cerebellar vermis, and with the astrocytomas the syndromes of the cerebellar hemisphere and of the frontal lobe. Pathology and symptomatology are so skilfully mingled that the final product is not only clear and coherent but also makes a fascinating study of a subject which is never an easy one, and which is too often treated in a dull and uninspiring fashion.

A chapter devoted to miscellaneous and metastatic tumours is followed by a most important discussion of general and differential diagnosis, and the last chapter gives a brief but comprehensive account of the principles which underlie the treatment of intracranial tumours. Technique is not described in detail, but many valuable hints are offered to guide the surgeon when he encounters the problems which still have to be tackled even after the tumour has been found.

The book is illustrated by pen-and-ink drawings which have little artistic merit, but what they lose in beauty they gain in clarity. Professor Bailey has already achieved distinction for his cytological and experimental researches, and he now proves that his clinical observations have kept pace with his laboratory studies. His book is a storehouse of valuable clinical observations, and the style is entertaining because the material was originally arranged for clinical demonstrations in the University of Chicago. It will be appreciated by students working for the higher degrees and diplomas in both medicine and surgery. All those who intend to make a special study of neurology will be well advised to master its contents, and even the most experienced may dip into it with much profit.

Surgery of the Stomach and Duodenum. By J. SHELTON HORSLEY, M.D., F.A.C.S., LL.D., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va. Royal 8vo. Pp. 260, with 136 illustrations. 1933. London: Henry Kimpton. 35s. net.

THIS monograph represents largely the personal experience of a well-known American surgeon and one widely recognized as entitled to speak with authority upon the subject with which it deals. The embryology, anatomy, and physiology of the stomach and duodenum are first described, and a successful attempt is made to correlate the known facts of physiology with the symptoms of gastric and duodenal affections and with the principles of their operative treatment. Stress is laid upon the motor functions, since their derangement is responsible for probably 80 per cent of all gastric symptoms. The essential motor government of the stomach and duodenum is mainly intrinsic and is "myogenic" in origin (Alvarez), although extrinsic nerve connections exert a regulating influence. Emptying of both stomach and small intestine is due to a "gradient of contraction" (Alvarez), which consists in a more rapid movement of the muscular apparatus of the proximal than of the distal portion.

In the section upon etiology the importance of the contact of acid gastric juice with the intestinal mucosa, of streptococcal infection, and of the influence of the nervous system are all duly considered, and attention is directed to the alleged differences between America and Europe with regard to the type of gastroduodenal lesions. A study of 3000 case histories of gastroduodenal lesions operated upon at the Mayo Clinic shows that at the end of five years the death-rate in the cases of gastric ulcer was two and a half times that of the normal rate, while that in the cases of duodenal ulcer was but little above the normal.

In the preparation of patients for operation Horsley is a strong advocate of the continuous intravenous infusion of dextrose in Ringer's solution, and an excellent description is given of the technique.

The various operative procedures upon the stomach and duodenum are carefully and succinctly detailed, the sections dealing with gastrostomy, pyloroplasty, and partial gastrectomy meriting special mention. Horsley has a poor opinion of cholecystogastrostomy ("gastric bilification") in the treatment of gastric ulcer, while he favours the addition of resection of the gastric vagus nerves to such other local procedures as may be indicated in the treatment of cases of recurrent peptic ulcers, as tending to diminish reflex pylorospasm. Jejunal ulcer following gastroenterostomy is well described, as are the various procedures for its relief. The work is well illustrated, most of the illustrations being new, and there is a good index.

Die Bluttransfusion. By Prof. Dr. OEHLECKER (Hamburg). Super royal 8vo. Pp. 87 + viii, with 43 illustrations. 1933. Berlin and Vienna. Urban & Schwarzenberg. Paper covers, RM. 4; bound RM. 5.20.

THE author complains that previous books on this subject have dealt too much with the actual transfusion of blood, relegating to a secondary place the more important consideration, hæmolysis. He gives a short survey of the development of intravenous therapy, and then proceeds directly to this question of hæmolysis and allied reactions. Chapters follow describing the determination of groups, sources of error, and choice of donors, occupying about one-half of the book. There remain descriptions of various techniques and the indications for transfusion of blood.

Professor Oehlecker lays great emphasis upon the strict differences between hæmolysis and other reactions. Clinical evidence of hæmolysis always occurs one to two minutes after the commencement of the transfusion. He considers the signs and symptoms absolutely characteristic of this condition, and never to be confused with late reactions, frequently associated with rigors; these have no relation to hæmolysis, but to the donor's plasma or impurities in the citrate, etc. In consequence, prior to Landsteiner's discovery of the blood groups, Oehlecker devised his 'biological test'—an assay of compatibility. This is now in constant use as an extra safeguard. The test is simplicity itself. Whilst an assistant retains his finger on the patient's pulse, the surgeon injects—intravenously—a small quantity

of the blood, 5 to 20 c.c., according to the condition of the patient. Some two minutes is allowed to elapse, and the procedure is repeated. In the absence of untoward symptoms the transfusion is completed in normal fashion. When incompatibility is present, the signs of hæmolysis will become apparent within the two minutes. They are akin to collapse, with pallor, falling-off of pulse, sweating, restlessness, and perhaps breathlessness. These somewhat alarming events rapidly subside without harmful effects. Before the introduction of blood grouping, which of course is now used as a routine measure in his clinic, Professor Oehlecker detected by this method among very many uneventful transfusions fifty cases of hæmolysis, with only one fatality. It appears therefore to be a reliable one, which may be adopted when a surgeon is driven to a transfusion without possessing means of grouping.

Some isolated points may be of interest. With an experience of 1000 transfusions, the author by no means objects to the repeated use of the same donor for the same recipient. Large quantities of blood are often of great value, from 1 to 1·5 litres. The professional donor in Münich receives 10 marks, in Berlin up to 20 marks, for each transfusion, and in New York 7 dollars per 100 c.c. of blood!

Of the various techniques, the indirect citrate method and his own are described in detail. The latter is a simple method by means of a syringe and two-way tap, of transferring whole blood directly from one person's vein to another, using intermittent irrigation with normal saline to avoid any clotting. It possesses the overwhelming disadvantage that on many surgical occasions close proximity of donor and patient is neither possible nor desirable. Professor Oehlecker draws his net far and wide in discussing the indications for transfusion. Few will differ from him, and it is interesting to note that in cases of acute staphylococcal or streptococcal septicæmia he does not consider a transfusion of any value; but of great help in the treatment of 'sepsis'. In acute pancreatic necrosis attention is drawn to the remarkable resuscitation which follows a large transfusion.

This short monograph is written in a clear style, in quite simple German, and is well worth reading. The author writes authoritatively from wide experience, and considers his subject from every aspect, supporting his arguments with personal cases and quotations from the literature.

Manuel de Radiodiagnostic clinique. By R. LEDOUX-LEBARD (Paris). Royal 8vo. In two volumes. Pp. 1075 + xvi, with 1143 illustrations. 1933. Paris: Masson et Cie. Fr. 260.

THIS is the best manual on radiology in the French language. It differs from other volumes in that art paper has been used throughout; consequently the radiographic illustrations, which have been well selected, are included in the text. It is not a mere atlas of pictures, but a descriptive account of the appearances which can be detected in disease on radiographic and radioscopic examination. The manual is published in two volumes and contains sections dealing with interpretation of radiographs and the localization of foreign bodies, the skeletal, nervous, circulatory, respiratory, digestive, and urinary systems, and the use of radiography in obstetrics and gynæcology. Unlike many former manuals on radiology, it does not contain long and tedious chapters on apparatus, which are for the most part culled from the pages of manufacturers' advertising publications. Some sections, notably those on the digestive, circulatory, and respiratory systems, are exhaustive and well illustrated. Interesting accounts and illustrations are given of the use of the more modern methods of radiographic investigation, including arteriography, ventriculography, pneumoperitoneum, cholecystography, intravenous pyelography, and lipiodol injections into the various tubular structures of the human anatomy.

The author and publishers are to be congratulated on the excellence of the illustrations and their reproduction. The volumes should be a valuable addition to the library of all radiologists.

Paralysis in Children. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (Ed.), Physician, Bath and Wessex Orthopædic Hospital, etc.; and M. FORRESTER-BROWN, M.D., M.S. (Lond.), Surgeon, Bath and Wessex Orthopædic Hospital, etc. Demy 8vo. Pp. 328 + viii, with 116 illustrations. 1933. London: Humphrey Milford. 15s. net.

THIS book represents the views of a neurologist and a surgeon, working together at an orthopædic centre for children where many cases of poliomyelitis and other paralytic conditions are admitted. The first part of the book deals with the general problems of paralysis, the physiology of movement, the location of the lesion which underlies the various syndromes described, the general pathology of paralysis, and the interpretation of symptoms. The second part is clinical and deals with muscular dystrophies, traumatic lesions of peripheral nerves, neuritis, juvenile tabes, anterior poliomyelitis, Landry's paralysis, Friedreich's ataxia, the cerebellar affections of childhood, disseminated sclerosis, striate lesions, spastic paralysis, chorea, and other types of paralysis. The third part deals with treatment, and is chiefly concerned with the various methods in the field of physiotherapy and non-operative orthopædics which have been used. Technical descriptions of operations are not given in any detail, except for some of the operations for the transplantation of tendons.

The book is certainly a most useful mine of information. Perhaps the sections on physiology are more profound than is necessary in a work of this kind. The chapters on re-education, the use of swimming exercises in warm water, and the adaptation of splints to paralysis are all most excellent, and the illustrations are very clear and well produced.

The Duodenum: Its Structure and Function, its Diseases and their Medical and Surgical Treatment. By EDWARD L. KELLOG, M.D., F.A.C.S., Professor of Surgery and formerly Professor of Gastro-enterology, N.Y. Polyclinic Medical School. Imperial 8vo. Pp. 855 + xxviii, with 287 illustrations. 1933. New York: Paul B. Hoeber Inc. $10.

THIS volume is described by the publishers as a monograph, but it is considerably bigger than a number of text-books devoted to the whole field of surgery. The author goes into very great detail, but nowhere does the subject seem to be unduly laboured. The work is based on twenty years of practice by the author and extracts from the literature, the extent of which can be judged by the fact that the references occupy 132 pages. The book commences with an account of the anatomy and physiology of the duodenum, together with chapters on its bacteriology and the methods used to examine it. The account of the X-ray examination is one of the best we have seen, but we cannot agree that a standard of perfection of such a degree has been reached that "it is unusual to demonstrate an ulcer at the operation table which the roentgenologist has failed to detect".

The first pathological condition to be dealt with is duodenitis, the importance and frequency of which is becoming more generally recognized. The author makes some interesting observations on the associated condition of duodenal glycosuria. Diverticula and duodenal ileus are well dealt with in separate chapters, and in both cases they are amplified by a number of clinical records.

Ulcer is naturally very fully considered, and it is a useful classification to look upon them as surgical, medical, and borderline cases. The methods of treating cases medically are considered in great detail together with the results which may be expected. It is a strong point in the book's favour that the author everywhere puts both sides of the case fairly and allows the reader to form his own judgements from them. We are glad to see that he deals with loss of liver dullness in perforation of ulcers by saying that it is probably rather infrequent. He goes on to qualify this by saying that it did not occur in a series of 100 cases on which he operated.

The surgical procedures are collected together into one chapter at the end of the book—an admirable arrangement which allows them to be referred to with the greatest of ease. They consist very largely of excellently reproduced drawings illustrating the operations, so that it is possible to follow them without referring to the text at all.

The production of the book is one on which the publishers are to be congratulated. The division of the index into subjects and proper names is perhaps a small point, but is one which makes for clearness. It is a most comprehensive book, and one which should be in the hands of every gastro-enterologist, whether physician or surgeon.

A Practical Medical Dictionary. By THOMAS LATHROP STEDMAN, A.M., M.D. Twelfth edition. Royal 8vo. Pp. 1256 + xii. Illustrated. 1933. London: Baillière, Tindall & Cox. 35s. net.

MEDICINE progresses rapidly, and doctors coin new words, which are often uncouth, more quickly than lexicographers can assimilate and explain them. No finality, therefore, is possible for a medical dictionary. Dr. T. L. Stedman, of New York, published the first edition of his *Practical Medical Dictionary* in 1908; the twelfth revised edition appeared in 1933. He has been fortunate in bringing so great a work to a successful issue. Mr. Henry Power and Dr. Leonard Sedgwick undertook a similar task for the New Sydenham Society in 1879. They carried it on courageously to the letter O, when the funds of the Society were exhausted and the rest of the alphabet had to be curtailed.

It is not possible to review a dictionary, but errors can be noted and suggestions offered for future editions. The errors are negligible. Thomas Bryant never received a knighthood, so the title appended to his name should be omitted. For additions it should be explained that 'brain' fever and 'low' fever were synonyms in the North of England for typhoid; 'Clutton's joints' should be mentioned, and it should be stated that 'Baker's cysts' are as often tuberculous as osteo-arthritic. 'Delbet's splint' as well as his sign should be described, and if 'Jackson's membrane' is mentioned, why is 'Lane's membrane' omitted? Aneurysms are 'wired' as well as bones, and to Woelfler's name should be added his 'islets'. 'Sciopody' is a convenient term for the monstrous growth of feet when children look as if they could shade themselves under their own soles. They were described by such old travellers as Sir John Mandeville long before they entered medicine. The recently published general index to the BRITISH JOURNAL OF SURGERY will provide Dr. Stedman with numerous additions to the thirteenth edition of his very useful and convenient dictionary, for the production of which we heartily wish him health and strength.

Surgical Anatomy. By GRANT MASSIE, M.B., M.S. (Lond.), F.R.C.S. (Eng.), Assistant Surgeon, Guy's Hospital, etc. Second edition. Medium 8vo. Pp. 458 + x, with 147 illustrations, many in colour. 1933. London: J. & A. Churchill. 18s. net.

THIS book certainly carries out what the author intended—"clothing the dry bones with life". The balance between anatomical detail and its surgical application is a happy one, and the subject matter seems well up to date.

We are not quite in agreement with the author on a number of subjects. The terminology used in describing the movements of the ankle is confusing. The description of the internal lateral ligament of the knee and the surface marking of the lateral sinus are both misleading. Many of the figures are not strictly accurate, such as that of the knee-joint (*Fig.* 127), in which the synovial membrane is represented as covering the articular cartilage. Other figures show so few points that it would seem unnecessary to include them. *Fig.* 4, for instance, representing subtemporal decompression, whilst perhaps justifiable in a text-book of operative surgery, seems waste of space in a book of this sort. *Fig.* 121, too, shows very little relevant to the lumbar plexus that could not have been set out in a list giving the roots from which the nerves arise. The best section in the book is that on the abdomen, and it is here, too, that the best illustrations are to be found. The inclusion of a chapter on the autonomic nervous system is a unique and stimulating addition which should prove useful.

In spite of a few small inaccuracies in text and figures the author is to be congratulated on the production of a book which should be of great use to senior students and to those who, after qualifying, wish to refresh quickly their knowledge of anatomy.

The Operative Story of Cleft Palate. By GEORGE MORRIS DORRANCE, M.D., F.A.C.S. (Philadelphia), assisted by ENAYAT SHIRAZY, D.D.S. Medium 8vo. Pp. 564 + x, with 534 illustrations. 1933. London and Philadelphia: W. B. Saunders Co. 32s. 6d. net.

No surgeon who is seriously interested in the surgery of cleft palate can afford to be without this excellent book by Dorrance, since nearly the whole of its 564 pages is devoted to a consideration of the literature of the subject. In a great many cases the original illustrations and some of the text of the various authors are copied *in extenso*. The magnitude of the labour can be judged from the bibliographical list, which runs into eighty-seven pages of the book, and it would appear as though the author had set himself the task of reviewing every paper that had ever been written on cleft palate.

The title of the book is somewhat misleading, in that the contents, although following a more or less chronological sequence, hardly constitute a story, but rather a complete catalogue—one which, nevertheless, is bound to remain for many years a standard work of reference.

It is only human that the author should finish his work with an account of his own operation, which, somewhat inappropriately, he styles the 'push-back' operation, whereas it is assumed that his aim is to free the soft tissues sufficiently to allow them to be pulled back by their own muscles; it is difficult to imagine soft tissues being pushed back. The push-back operation is strongly recommended by its author as the method of choice, but he has, unfortunately, followed a great many of those who write on this subject, and failed to record the number of cases on which he has operated, the mortality if any, the number of those in whom he has restored the palatopharyngeal sphincter and the evidence on which this is based, and, above all, the speech results and the standard of speech he regards as being good, bad, or indifferent; the example of Victor Veau must have been constantly before him since he uses some Veau methods.

The illustrations throughout are excellent, but unfortunately some of them cannot be accepted seriously, e.g., *Fig.* 518 cannot by any stretch of imagination be said to present evidence of the restoration of the palatopharyngeal sphincter, since it was shown years ago that the appearance of the palate, as viewed from below, was no indication of velopharyngeal competence.

As a work of reference, the book is indispensable; but that part devoted to Dorrance's own opinions and methods requires more than his bald dogmatism before it can be generally accepted.

The Radiology of Bones and Joints. By JAMES F. BRAILSFORD, M.D.(B'ham), M.R.C.S. (Eng.), Radiologist, Queen's Hospital, Birmingham, etc. $9\frac{3}{4} \times 7$ in. Pp. 500 + xx, with 310 illustrations. 1934. London: J. & A. Churchill. 30s. net.

THIS is a very valuable book, and in producing it Dr. Brailsford has made a most necessary contribution to radiology. Notwithstanding the title of the book it deals almost entirely with diseases of the bones and joints, fractures having been given very scanty consideration. This is probably a wise decision, because there are nearly five hundred pages. The author has discussed the various anatomical regions separately, and this will be found a great advantage in making references. Most conditions, both rare and common, have been dealt with as fully as possible, and a very full bibliography is given to enable a reader to make further study.

It is not a criticism to say that one would like to see a wider discourse on the radiographic manifestations of tuberculous affections of the joints, for this is a most important part of a radiologist's work and one which yields unsatisfactory results in a large number of cases. The recent work of Allison and Ghormley has emphasized the limitations of radiography in the diagnosis of joint disease.

The reproductions are plentiful, and on the whole good, but there are some which would have been more descriptive had they been larger. Dr. Brailsford is to be congratulated, and his work should find a wide circle of readers.

The Surgery of the Sympathetic Nervous System. By GEORGE E. GASK, C.M.G., D.S.O., F.R.C.S., Professor of Surgery, University of London, etc.; and J. PATERSON ROSS, M.S.(Lond.), F.R.C.S., Reader in Surgery, University of London, etc. Imperial 8vo. Pp. 163 + xii, with 13 plates and 30 other illustrations. 1934. London: Baillière, Tindall & Cox. 16s. net.

OUR only quarrel with this book lies in its title. An account of the many directions in which the surgery of the autonomic nervous system is going forward is hardly to be undertaken at this time and compressed within the scanty limit of 159 pages, however well written they might be. Subject to this limitation, and considering the fact that the authors' personal experience is confined to relatively few cases, the work has been extraordinarily well done. Regarded as a critical summary of the present state of our knowledge in the commoner applications of sympathectomy the book is admirable. The difficult subject of anatomy and physiology is clearly and thoroughly well described, whilst, following this, the preliminary investigations, so important before operation, are comprehensively and helpfully outlined. Throughout the remaining chapters, which deal with disorders of the circulation, disorders of the visceral motor mechanism, and with pain, the authors have given a summary in which the criticism is always keen and fair and the judgement exceptionally sound and restrained.

We note a tendency to regard the results of sympathectomy in thrombo-angiitis obliterans a little more hopefully than was done in the Bradshaw Lecture of 1932, and we would criticize the account of the parasympathetic supply to the distal colon as an inaccurate report of Stopford's original description.

In the surgery of the autonomic system the time factor is the great difficulty in the assessment of results. The present revival of interest in this branch must wait some years before definite statements can be made. The question of relapse is a very real one and further information is necessary on the recovery of intrinsic function of organs deprived of their sympathetic supply. These criticisms are not intended in any way to detract from the value of this book, and we should like to state how much we have appreciated the clear-cut and fair presentation which it gives. Any surgeon who may be contemplating an incursion into this difficult and largely uncharted field must have this book. He will find throughout its pages a guidance always safe and helpful.

Chirurgie infantile d'Urgence. By M. FEVRE, Ancien Chef de Clinique chirurgicale infantile, Chirurgien des Hôpitaux de Paris. Preface by Professor OMBRÉDANNE. Large royal 8vo. Pp. 452, with 110 illustrations. 1933. Paris: Masson et Cie. Fr. 70.

THIS is a comprehensive volume dealing with every aspect of emergency surgery in childhood. In the main the teaching is similar to that practised in this country; there are, however, several exceptions. High tracheotomy is advised in all cases of obstruction, and an ancient type of coin-catcher is used to remove small coins from the œsophagus. This form of treatment has surely been replaced by direct removal by means of an œsophagoscope even in children. The author is very optimistic with regard to the treatment of the various kinds of spina bifida, the final result of which is too often hydrocephalus.

The illustrations are good on the whole, but it is a pity that a book devoted to emergency surgery in children should depict figures of adult patients. The index is small and incomplete for such a volume.

BOOK NOTICES.

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest for our readers.]

On Osteogenic Sarcoma. By JACOB VAN DER SPEK (Amsterdam). Royal 8vo. Pp. 219. Illustrated. 1933. Kemink en zoon N.V.—Over Den Dom—Utrecht.

The Spread of Tumours in the Human Body. By RUPERT A. WILLIS, M.D., B.S., D.Sc., Melbourne, Pathologist to the Alfred Hospital and to the Austin Hospital for Chronic Diseases, Melbourne. Demy 8vo. Pp. 540 + x, with 103 illustrations. 1934. London: J. & A. Churchill. 25s. net.

Infections of the Hand. By ALLEN B. KANAVEL, M.D., Sc.D., Professor of Surgery, North-western Medical School, Chicago. Sixth edition. Medium 8vo. Pp. 552 + xvi, with 216 illustrations. 1934. London: Baillière, Tindall & Cox. 30s. net.

St. Bartholomew's Hospital Reports. Edited by LORD HORDER, R. G. CANTI, W. SHAW, C. F. HARRIS, H. H. WOOLARD, R. C. ELMSLIE, W. G. BALL, G. EVANS, and J. P. ROSS. Vol. LXVI. Demy 8vo. Pp. 363 + xxiv. Illustrated. 1933. London: John Murray. 21s. net.

L'Artériectomie dans les Artérites oblitérantes. By RENÉ LERICHE, Professeur à la Faculté de Médecine de Lyon; and PIERRE STRICKER, Ancien Chef de Clinique à la Faculté de Médecine de Strasbourg. Large 8vo. Pp. 198, with 78 illustrations. 1933. Paris: Masson et Cie. Fr. 40.

Gelenksteifen und Gelenkplastik. By Professor Dr. ERWIN PAYR (Leipzig). Vol. I. 11 × 8 in. Pp. 880 + xiv, with 240 illustrations. 1934. Berlin: Julius Springer. Paper covers, RM. 120; bound, RM. 124.80.

La Sténose hypertrophique du Pylore chez le Nourisson. By J. POUCEL, Chirurgien des Hôpitaux de Marseille. $7\frac{3}{4}$ × 5 in. Pp. 108 + viii, with 16 illustrations in the text and 8 plates. 1934. Paris: Masson et Cie. Fr. 20.

Lessons on the Surgical Diseases of Childhood. By WILLIAM RANKIN, M.B., Ch.B. Royal 8vo. Pp. 190. Illustrated. 1934. Glasgow: Alex. MacDougall. 21s. net.

A Short History of Some Common Diseases. Edited by W. R. BETT, M.R.C.S., L.R.C.P. Demy 8vo. Pp. 211. London: Humphrey Milford. 10s. 6d. net.

Il Cancro del Retto. By VITTORIO PETTINARI. Crown 4to. Pp. 225 + iv, with 121 illustrations. 1934. Bologna: Licinio Cappelli. L. 30.

Operating Room Procedure: For Nurses and Internes. By HENRY C. FALK, M.D., F.A.C.S., Clinical Professor of Gynæcology, New York University and Bellevue Hospital Medical College, etc. With a Foreward by EUGENE H. POOL, M.D., New York. Large 8vo. Pp. 413 + xxii, with 328 illustrations. 1934. New York and London: G. P. Putnam's Sons. $3.00.

Die moderne Finsenbehandlung. By DR. SVEND LOMHOLT (Copenhagen). Large 8vo. Pp. 64. Illustrated. 1934. Berlin and Vienna: Urban and Schwarzenberg.

Trattato di Patologia chirurgica generale e speciale. By Prof. OTTORINO UFFREDUZZI (Turin). Vol. II. Pp. 1199 + viii, with 25 plates and 448 illustrations. 1934. Turin: Unione Tipografico-Editrice Troninence. Lire 145.

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